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**WO 02/34721 A1**

(54) Title: **ACYLSEMICARBAZIDES AND THEIR USE AS CYCLIN DEPENDENT KINASE (CDK) INHIBITORS**

(57) Abstract: The present invention relates to the synthesis of a new class of indeno [1,2-c]pyrazol-4-ones of formula (I): that are potent inhibitors of the class of enzymes known as cyclin dependent kinases, which relate to the catalytic subunits cdk1-9 and their regulatory subunits known as cyclins A-H. The invention also provides a novel method of treating cancer or other proliferative disease by administering a therapeutically effective amount of one of these compounds or a pharmaceutically acceptable salt form thereof. Alternatively, one can treat cancer or other proliferative disease by administering a therapeutically effective combination of one of the compounds of the present invention and one or more other known anti-cancer or anti-proliferative agents.

5

TITLE

ACYLSEMICARBAZIDES AND THEIR USE AS CYCLIN DEPENDENT KINASE (CDK) INHIBITORS

FIELD OF THE INVENTION

This invention relates generally to novel 5-substituted-indeno[1,2-c]pyrazol-4-ones which are useful as cyclin dependent kinase (cdk) inhibitors, pharmaceutical compositions comprising the same, kits and methods for using the same for treating proliferative diseases, and intermediates and processes for making the same.

15

BACKGROUND OF THE INVENTION

One of the most important and fundamental processes in biology is the division of cells mediated by the cell cycle. This process ensures the controlled production of subsequent generations of cells with defined biological function. It is a highly regulated phenomenon and responds to a diverse set of cellular signals both within the cell and from external sources. A complex network of tumor promoting and suppressing gene products are key components of this cellular signaling process. Over expression of the tumor promoting components or the subsequent loss of the tumor suppressing products will lead to unregulated cellular proliferation and the generation of tumors (Pardee, Science 246:603-608, 1989).

Cyclin dependent kinases (cdks) play a key role in regulating the cell cycle machinery. These complexes consist of two components: a catalytic subunit (the kinase) and a regulatory subunit (the cyclin). To date, nine kinase subunits (cdk 1-9) have been identified along with several regulatory subunits (cyclins A-H) (A.M. Senderowicz and E.A. Sausville Journal of the National Cancer Institute (2000), 92 (5), 376-387; S. Mani; C. Wang; K. Wu; R. Francis; R.

- 5 Pestell Exp. Opin. Invest. Drugs (2000) 9(8), 1849-1870;  
Brizuela, Leonardo; Gyuris, Jenő; Mansuri, Muzammil, Princ.  
Mol. Oncol. (2000), 197-236; Fry, David W.; Garrett,  
Michelle Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs  
(2000), 2(1), 40-59).
- 10 Each kinase associates with a specific regulatory  
partner and together make up the active catalytic moiety.  
Each transition of the cell cycle is regulated by a  
particular cdk complex: G1/S by cdk2/cyclin E, cdk4/cyclin  
D1 and cdk6/cyclinD2; S/G2 by cdk2/cyclin A and cdk1/cyclin  
15 A; G2/M by cdk1/B. The coordinated activity of these kinases  
guides the individual cells through the replication process  
and ensures the vitality of each subsequent generation  
(Sherr, Cell 73:1059-1065, 1993; Draetta, Trends Biochem.  
Sci. 15:378-382, 1990)
- 20 An increasing body of evidence has shown a link between  
tumor development and cdk related malfunctions. Over  
expression of the cyclin regulatory proteins and subsequent  
kinase hyperactivity have been linked to several types of  
cancers (Jiang, Proc. Natl. Acad. Sci. USA 90:9026-9030,  
25 1993; Wang, Nature 343:555-557, 1990). More recently,  
endogenous, highly specific protein inhibitors of cdks were  
found to have a major affect on cellular proliferation (Kamb  
et al, Science 264:436-440, 1994; Beach, Nature 336:701-704,  
1993). These inhibitors include p16<sup>INK4</sup> (an inhibitor of  
30 cdk4/D1), p21<sup>CIP1</sup> (a general cdk inhibitor), and p27<sup>KIP1</sup> (a  
specific cdk2/E inhibitor). A recent crystal structure of  
p27 bound to cdk2/A revealed how these proteins effectively  
inhibit the kinase activity through multiple interactions  
with the cdk complex (Pavletich, Nature 382:325-331, 1996).
- 35 These proteins help to regulate the cell cycle through  
specific interactions with their corresponding cdk  
complexes. Cells deficient in these inhibitors are prone to  
unregulated growth and tumor formation.

5 Protein kinases, in particular, CDK, play a role in  
the regulation of cellular proliferation. Therefore, CDK  
inhibitors could be useful in the treatment of cell  
proliferative disorders such as cancer, familial  
adenomatosis polyposis, neuro-fibromatosis, psoriasis,  
10 fungal infections, endotoxic shock, trasplantaion rejection,  
vascular smooth cell proliferation associated with  
atherosclerosis, pulmonary fibrosis, arthritis  
glomerulonephritis and post-surgical stenosis and restenosis  
(U.S. Patent No. 6,114,365).

15 CDKs are also known to play a role in apoptosis.  
Therefore CDK inhibitors, could be useful in the treatment  
of useful of cancer; viral infections, for example,  
herpevirus, poxvirus, Epstein-Barr virus, Sindbis virus and  
adenovirus; prevention of AIDS development in HIV-infected  
20 individuals; autoimmune diseases, for example, systemic  
lupus, erythematosus, autoimmune mediated  
glomerulonephritis, rheumatoid arthritis, psoriasis,  
inflammatory bowel disease, and autoimmune diabetes  
mellitus; neurodegenerative disorders, for example,  
25 Alzheimer's disease, AIDS-related dementia, Parkinson's  
disease, amyotrophic lateral sclerosis, retinitis  
pigmentosa, spinal muscular atrophy and cerebellar  
degeneration; myelodysplastic syndromes, aplastic anemia,  
ischemic injury associated with myocardial infarctions,  
30 stroke and reperfusion injury, arrhythmia, atherosclerosis,  
toxin-induced or alcohol related liver diseases,  
hematological diseases, for example, chronic anemia and  
aplastic anemia; degenerative diseases of the  
musculoskeletal system, for example, osteoporosis and  
35 arthritis, aspirin-sensitive rhinosinusitis, cystic  
fibrosis, multiple sclerosis, kidney diseases and cancer  
pain (U.S. Patent No. 6,107,305).

It has also been discovered that some cyclin-dependent  
kinase inhibitors can be used in combination therapy with  
40 other anticancer agents. For example, the cytotoxic  
activity of the cyclin-dependent kinase inhibitor,  
flavopiridol, has been used with other anticancer agents in



5 cancer combination therapy. Cancer Research, 57, 3375 (1997).

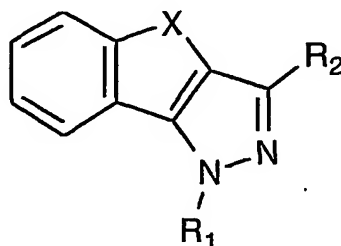
Also, it has recently been disclosed that CDK inhibitors may be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of  
10 invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse (U.S. Patent No. 6,107,305).

Furthermore, it has recently been discovered that cdk5  
15 is involved in the phosphorylation of tau protein, and therefore CDK inhibitors may be useful in the treatment of Alzheimer's disease (J. Biochem., 117, 741-749, 1995).

This body of evidence has led to an intense search for small molecule inhibitors of the cdk family as an approach  
20 to cancer chemotherapy. There are no known examples of molecules related to the current invention which describe 5-substituted-indeno[1,2-c]pyrazoles as cdk inhibitors. There is one case describing indeno[1,2-c]pyrazoles having anticancer activity. There are two other examples which  
25 describe indeno[1,2-c]pyrazoles having unrelated utilities and structures.

A series of indeno[1,2-c]pyrazoles having anticancer activity are described in JP 60130521 and JP 62099361 with the following generic structure:

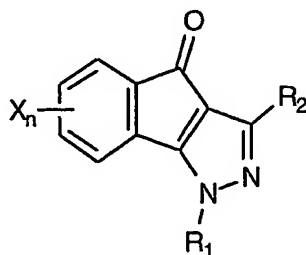
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No substitution is claimed on the indenophenyl portion of the molecule and the molecules are not indicated to be cdk

5 inhibitors. In addition, we discovered that substitution at the 5-position was critical for cdk inhibitory activity.

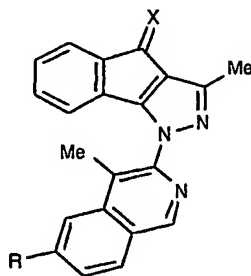
A series of indeno[1,2-c]pyrazoles having herbicidal activity are described in GB 2223946 with the following generic structure:



10

wherein  $X_n$  is defined as halo, alkyl, haloalkyl, and haloalkoxy;  $n = 0-2$ . In addition,  $R_1$  is defined as acyl and  $R_2$  is defined as alkyl or cycloalkyl.

15 A series of 1-(6'-substituted-4'-methylquinol-2'-yl)-3-methylindeno[1,2-c]pyrazoles having CNS activity are described by Quraishi, Farmaco 44:753-8, 1989 with the following generic structure:



20

Compounds of this series are not considered to be part of the presently claimed invention.

25

#### SUMMARY OF THE INVENTION

The present invention describes a novel class of indeno[1,2-c]pyrazol-4-ones or pharmaceutically acceptable

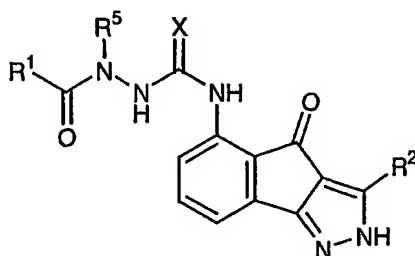
5 salt forms thereof that are potent inhibitors of the class of enzymes known as cyclin dependent kinases, which relate to the catalytic subunits cdk 1-9 and their regulatory subunits known as cyclins A-H.

10 It is another object of this invention to provide a novel method of treating proliferative diseases associated with CDK activity by administering a therapeutically effective amount of one of the compounds of the invention or a pharmaceutically acceptable salt form thereof.

15 It is another object of this invention to provide a novel method of treating cancer associated with CDK activity by administering a therapeutically effective amount of one of the compounds of the invention or a pharmaceutically acceptable salt form thereof.

20 It is another object of this invention to provide a novel method of treating a proliferative disease, which comprises administering a therapeutically effective combination of one of the compounds of the present invention and one or more other known anti-cancer treatments such as radiation therapy, chemotoxic or chemostatic agents.

25 These and other objectives have been achieved by the inventors' discovery that compounds of formula (I):



30

(I)

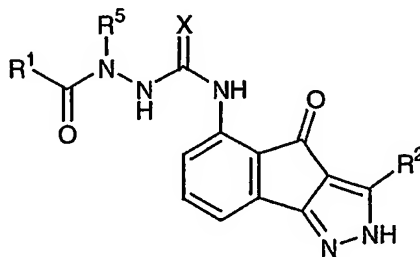
5 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>5</sup> and X are defined below or  
pharmaceutically acceptable salts thereof are cyclin  
dependent kinase inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

10 The invention pertains to novel cyclin dependent kinase  
inhibitors (cdks) and specifically, but not exclusively, as  
inhibitors of cdk/cyclin complexes. The inhibitors of this  
invention are indeno[1,2-c]pyrazol-4-one analogs. Certain  
analogues were selective for their activity against cdks and  
15 their cyclin bound complexes and were less active against  
other known serine/threonine kinases such as Protein Kinase  
A (PKA) and Protein Kinase C (PKC).

As described herein, the inhibitors of this invention  
are capable of inhibiting the cell-cycle machinery and  
20 consequently would be useful in modulating cell-cycle  
progression, which would ultimately control cell growth and  
differentiation. Such compounds would be useful for treating  
subjects having disorders associated with excessive cell  
proliferation, such as the treatment of cancer, psoriasis,  
25 immunological disorders involving unwanted leukocyte  
proliferation, in the treatment of restinosis and other  
smooth muscle cell disorders, and the like.

(1) The present invention, in a first embodiment, describes  
30 a novel compound of formula (I):



5 X is O or S;

$R^1$  is  $-NR^3R^{3a}$ ,  $-CF_3$ ,  $C_{1-4}$  alkyl substituted with 1-3  $R^4$ ,  $C_{5-10}$  alkyl substituted with 0-3  $R^4$ ,  $C_2-C_{10}$  alkenyl substituted with 0-3  $R^4$ ,  $C_2-C_{10}$  alkynyl substituted with 0-3  $R^4$ ,  $C_3-C_{10}$  carbocycle substituted with 0-5  $R^6$ ,  
 10 or 5-10 membered heterocycle substituted with 0-3  $R^6$ ;  
 provided that if  $R^1$  is phenyl or benzyl, then  $R^1$  is substituted with 1-5  $R^6$ ;

$R^2$  is H,  $C_{1-10}$  alkyl substituted with 0-3  $R^7$ ,  $C_{2-10}$  alkenyl substituted with 0-3  $R^7$ ,  $C_{2-10}$  alkynyl substituted with  
 15 0-3  $R^7$ ,  $-CF_3$ ,  $C_{3-10}$  carbocycle substituted with 0-5  $R^8$ ,  
 or 3-10 membered heterocycle substituted with 0-5  $R^8$ ;

$R^3$  and  $R^{3a}$  are independently selected from the group: H,  $C_{1-4}$  alkyl, phenyl and benzyl;

$R^4$  and  $R^7$  are, at each occurrence, independently selected  
 20 from the group: halo,  $-CN$ ,  $NO_2$ ,  $-NR^9R^{9a}$ ,  $NR^9NR^{9a}R^{9b}$ ,  
 $NR^9C(O)OR^{10}$ ,  $NR^9C(O)R^{10}$ ,  $=O$ ,  $OR^{10}$ ,  $SR^{10}$ ,  $-CF_3$ ,  $COR^{10}$ ,  
 $CO_2R^{10}$ ,  $CONR^9R^{9a}$ ,  $NHC(O)NR^9R^{9a}$ ,  $NHC(S)NR^9R^{9a}$ ,  
 $SO_2NR^9R^{9a}$ ,  $SO_2R^{10}$ ,  $C_{3-10}$  carbocycle substituted with  
 0-5  $R^{11}$ , and 5-10 membered heterocycle substituted with  
 25 0-3  $R^{11}$ ;

$R^5$  is selected from the group: H,  $-C(O)R^{12}$ ,  $-C(O)OR^{12}$ ,  $C_{1-4}$  alkyl, phenyl and benzyl;

$R^6$  and  $R^8$  are, at each occurrence, independently selected  
 from the group: halo,  $-CN$ ,  $NO_2$ ,  $C_{1-4}$  alkyl,  $C_{1-4}$   
 30 haloalkyl,  $NR^{13}R^{13a}$ ,  $NR^{13}NR^{13a}R^{13b}$ ,  $NR^{13}C(O)OR^{14}$ ,  
 $NR^{13}C(O)R^{14}$ ,  $=O$ ,  $OR^{14}$ ,  $SR^{14}$ ,  $-CF_3$ ,  $COR^{14}$ ,  $CO_2R^{14}$ ,  
 $CONR^{13}R^{13a}$ ,  $NHC(O)NR^{13}R^{13a}$ ,  $NHC(S)NR^{13}R^{13a}$ ,

- 5         $\text{SO}_2\text{NR}^{13}\text{R}^{13a}$ ,  $\text{SO}_2\text{R}^{14}$ , C<sub>3-10</sub> carbocycle substituted with  
0-5  $\text{R}^{15}$ , and 5-10 membered heterocycle substituted with  
0-3  $\text{R}^{15}$ , or when two  $\text{R}^{6s}$  or  $\text{R}^{8s}$  are attached to two  
adjacent carbon atoms, the two  $\text{R}^{6s}$  or  $\text{R}^{8s}$  may combine  
to form  $-\text{OCH}_2\text{O}-$  or  $-\text{OCH}_2\text{CH}_2\text{O}-$ ;
- 10     $\text{R}^9$  is, at each occurrence, independently selected from the  
group: H,  $-\text{C}(\text{O})\text{R}^{12}$ ,  $-\text{C}(\text{O})\text{OR}^{12}$ , C<sub>1-4</sub> alkyl, phenyl and  
benzyl;
- $\text{R}^{9b}$  is, at each occurrence, independently selected from the  
group: H,  $-\text{C}(\text{O})\text{R}^{12}$ ,  $-\text{C}(\text{O})\text{OR}^{12}$ , C<sub>1-4</sub> alkyl, phenyl and  
15    benzyl; or
- $\text{R}^9$  and  $\text{R}^{9a}$ , together with the nitrogen atom to which they  
are attached, form a heterocycle substituted with 0-3  
 $\text{R}^{16}$ ;
- $\text{R}^{9a}$  is selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and  
20    benzyl;
- $\text{R}^{10}$ ,  $\text{R}^{14}$ ,  $\text{R}^{17}$  are, at each occurrence, independently selected  
from the group: H, C<sub>1-4</sub> alkyl, phenyl, benzyl;
- $\text{R}^{11}$  is, at each occurrence, independently selected from the  
group: halo,  $-\text{CN}$ ,  $\text{NO}_2$ , C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl,  
25     $\text{NR}^{18}\text{R}^{18a}$ ,  $\text{NR}^{18}\text{NR}^{18a}\text{R}^{18b}$ ,  $\text{NR}^{18}\text{C}(\text{O})\text{OR}^{17}$ ,  $\text{NR}^{18}\text{C}(\text{O})\text{R}^{17}$ ,  $=\text{O}$ ,  
 $\text{OR}^{17}$ ,  $\text{SR}^{17}$ ,  $\text{COR}^{17}$ ,  $\text{CO}_2\text{R}^{17}$ ,  $\text{CONR}^{18}\text{R}^{18a}$ ,  $\text{NHC}(\text{O})\text{NR}^{18}\text{R}^{18a}$ ,  
 $\text{NHC}(\text{S})\text{NR}^{18}\text{R}^{18a}$ ,  $\text{SO}_2\text{NR}^{18}\text{R}^{18a}$ ,  $\text{SO}_2\text{R}^{17}$ , C<sub>3-10</sub> carbocycle  
substituted with 0-5  $\text{R}^{19}$ , and 5-10 membered heterocycle  
substituted with 0-3  $\text{R}^{19}$ ;

- 5 R<sup>13</sup> is, at each occurrence, independently selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and benzyl;
- R<sup>13a</sup> is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl; or
- 10 R<sup>13</sup> and R<sup>13a</sup>, together with the nitrogen atom to which they are attached, form a heterocycle substituted with 0-3 R<sup>16</sup>;
- R<sup>13b</sup> is, at each occurrence, independently selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and
- 15 benzyl;
- R<sup>15</sup>, R<sup>16</sup> and R<sup>19</sup> are, at each occurrence, independently selected from the group: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, NR<sup>20</sup>R<sup>20a</sup>, NR<sup>20b</sup>NR<sup>20</sup>R<sup>20a</sup>, NR<sup>20</sup>C(O)OR<sup>21</sup>, NR<sup>20</sup>C(O)R<sup>21</sup>, =O, OR<sup>21</sup>, SR<sup>21</sup>, COR<sup>21</sup>, CO<sub>2</sub>R<sup>21</sup>, CONR<sup>20</sup>R<sup>20a</sup>,
- 20 NHC(O)NR<sup>20</sup>R<sup>20a</sup>, NHC(S)NR<sup>20</sup>R<sup>20a</sup>, SO<sub>2</sub>NR<sup>20</sup>R<sup>20a</sup>, SO<sub>2</sub>R<sup>21</sup>, or when two R<sup>15</sup>s, R<sup>16</sup>s or R<sup>19</sup>s are attached to two adjacent carbon atoms, the two R<sup>15</sup>s R<sup>16</sup>s or R<sup>19</sup>s may combine to form -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-;
- R<sup>18</sup> is, at each occurrence, independently selected from the
- 25 group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and benzyl;
- R<sup>18a</sup> is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl; or
- R<sup>18</sup> and R<sup>18a</sup>, together with the nitrogen atom to which they
- 30 are attached, form a heterocycle substituted with 0-3 R<sup>19</sup>;

5 R<sup>18b</sup> is, at each occurrence, independently selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and benzyl; or

R<sup>20</sup> is, at each occurrence, independently selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and  
10 benzyl;

R<sup>20a</sup> is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;

R<sup>20b</sup> is, at each occurrence, independently selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and  
15 benzyl; and

R<sup>12</sup> and R<sup>21</sup> are, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl, benzyl; or a pharmaceutically acceptable salt form thereof, a pharmaceutically acceptable prodrug form thereof, an N-oxide  
20 form thereof, or a stereoisomer thereof.

(2) Another embodiment of the invention is a compound of embodiment (1) wherein:

X is O or S;

25 R<sup>1</sup> is -NR<sup>3</sup>R<sup>3a</sup>, -CF<sub>3</sub>, C<sub>1-4</sub> alkyl substituted with 1-3 R<sup>4</sup>, C<sub>2-4</sub> alkenyl substituted with 0-3 R<sup>4</sup>, C<sub>2-4</sub> alkynyl substituted with 0-3 R<sup>4</sup>, C<sub>3-10</sub> carbocycle substituted with 0-5 R<sup>6</sup>, or 5-10 membered heterocycle substituted with 0-3 R<sup>6</sup>.

30

(3) Another embodiment of the invention is a compound of embodiment (1) wherein:

X is O or S;



5  $R^1$  is  $-NR^3R^{3a}$ ,  $-CF_3$ , C1-C4 alkyl substituted with 1-3  $R^4$ ,  
C2-C4 alkenyl substituted with 0-3  $R^4$ , C2-C4 alkynyl  
substituted with 0-3  $R^4$ , C3-C6 carbocycle substituted  
with 0-5  $R^6$ , or 5-7 membered heterocycle substituted  
with 0-3  $R^6$ .

10

(4) Another embodiment of the invention is a compound of  
embodiment (1) wherein:

$R^1$  is C3-C6 saturated carbocycle substituted with 0-5  $R^6$ , or  
5-7 membered saturated heterocycle substituted with 0-3  
15  $R^6$ .

(5) Another embodiment of the invention is a compound of  
embodiment (1) wherein:

$R^1$  is C5-C6 partially saturated carbocycle substituted with  
20 0-5  $R^6$ , or 5-7 membered partially saturated heterocycle  
substituted with 0-3  $R^6$ .

(6) Another embodiment of the invention is a compound of  
embodiment (1) wherein:

25  $R^1$  is phenyl substituted with 1-5  $R^6$ , naphthyl substituted  
with 0-5  $R^6$ , or 5-6 membered aromatic heterocycle  
substituted with 0-3  $R^6$ .

(7) Another embodiment of the invention is a compound of  
30 embodiment (1) wherein:

$R^1$  is phenyl substituted with 1-3  $R^6$ , naphthyl substituted  
with 0-3  $R^6$ , or 5-6 membered aromatic heterocycle  
substituted with 0-3  $R^6$ .

5

(8) Another embodiment of the invention is a compound of embodiment (1) wherein:

$R^1$  is  $C_3$ - $C_{10}$  carbocycle substituted with 0-5  $R^6$ , or 5-10 membered heterocycle substituted with 0-3  $R^6$ ;

10  $R^6$  is, at each occurrence, independently selected from the group: halo, -CN,  $NO_2$ ,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $NR^{13}R^{13a}$ ,  $NR^{13}NR^{13a}R^{13b}$ ,  $NR^{13}C(O)OR^{14}$ ,  $NR^{13}C(O)R^{14}$ , =O,  $OR^{14}$ ,  $SR^{14}$ , - $CF_3$ ,  $COR^{14}$ ,  $CO_2R^{14}$ ,  $CONR^{13}R^{13a}$ ,  $NHC(O)NR^{13}R^{13a}$ ,  $NHC(S)NR^{13}R^{13a}$ ,  $SO_2NR^{13}R^{13a}$ , and  
15  $SO_2R^{14}$ , or when two  $R^{6s}$  are attached to two adjacent carbon atoms, the two  $R^{6s}$  may combine to form - $OCH_2O$ - or - $OCH_2CH_2O$ -.

(9) Another embodiment of the invention is a compound of embodiment (1) wherein:

20  $R^6$  is, at each occurrence, independently selected from the group: halo, -CN,  $NO_2$ ,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $NR^{13}R^{13a}$ ,  $NR^{13}NR^{13a}R^{13b}$ ,  $NR^{13}C(O)OR^{14}$ ,  $NR^{13}C(O)R^{14}$ , =O,  $OR^{14}$ ,  $SR^{14}$ , - $CF_3$ ,  $COR^{14}$ ,  $CO_2R^{14}$ ,  $CONR^{13}R^{13a}$ ,  
25  $NHC(O)NR^{13}R^{13a}$ ,  $NHC(S)NR^{13}R^{13a}$ ,  $SO_2NR^{13}R^{13a}$ , and  $SO_2R^{14}$ , or when two  $R^{6s}$  are attached to two adjacent carbon atoms, the two  $R^{6s}$  may combine to form - $OCH_2O$ - or - $OCH_2CH_2O$ -;

$R^{13}$ ,  $R^{13a}$  and  $R^{13b}$  are, at each occurrence, independently  
30 selected from the group: H,  $C_{1-4}$  alkyl, phenyl and benzyl; and

- 5 R<sup>14</sup> is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl, and benzyl.

(10) Another embodiment of the invention is a compound of embodiment (1) wherein:

- 10 R<sup>6</sup> is independently at each occurrence selected from the group: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, NR<sup>13</sup>R<sup>13a</sup>, NR<sup>13</sup>C(O)OR<sup>14</sup>, NR<sup>13</sup>C(O)R<sup>14</sup>, OR<sup>14</sup>, SR<sup>14</sup>, -CF<sub>3</sub>, COR<sup>14</sup>, CO<sub>2</sub>R<sup>14</sup>, CONR<sup>13</sup>R<sup>13a</sup>, NHC(S)NR<sup>13</sup>R<sup>13a</sup>, SO<sub>2</sub>NR<sup>13</sup>R<sup>13a</sup>, and SO<sub>2</sub>R<sup>14</sup>;
- 15 R<sup>13</sup>, R<sup>13a</sup> and R<sup>13b</sup> are each independently selected from the group: H or methyl; and
- R<sup>14</sup> is independently selected from the group: H, methyl, phenyl, and benzyl.

- 20 (11) Another embodiment of the invention is a compound of embodiment (1) wherein:

X is O or S;

R<sup>1</sup> is -NR<sup>3</sup>R<sup>3a</sup>, -CF<sub>3</sub>, C<sub>1-4</sub> alkyl substituted with 1-3 R<sup>4</sup>;

- R<sup>4</sup> is, at each occurrence, independently selected from the group: halo, -CN, NO<sub>2</sub>, -NR<sup>9</sup>R<sup>9a</sup>, NR<sup>9</sup>NR<sup>9a</sup>R<sup>9b</sup>, NR<sup>9</sup>C(O)OR<sup>10</sup>, NR<sup>9</sup>C(O)R<sup>10</sup>, =O, OR<sup>10</sup>, SR<sup>10</sup>, -CF<sub>3</sub>, COR<sup>10</sup>, CO<sub>2</sub>R<sup>10</sup>, CONR<sup>9</sup>R<sup>9a</sup>, NHC(O)NR<sup>9</sup>R<sup>9a</sup>, NHC(S)NR<sup>9</sup>R<sup>9a</sup>, SO<sub>2</sub>NR<sup>9</sup>R<sup>9a</sup>, and SO<sub>2</sub>R<sup>10</sup>;
- 25

- R<sup>9</sup> is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;
- 30

R<sup>9a</sup> is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;

- 5  $R^{9b}$  is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl; or  $R^9$  and  $R^{9a}$ , together with the nitrogen atom to which they are attached, form a 5-7 membered heterocycle substituted with 0-3  $R^{16}$ ;
- 10  $R^{16}$  is, at each occurrence, independently selected from the group consisting of: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl,  $NR^{20}R^{20a}$ ,  $NR^{20b}NR^{20}R^{20a}$ ,  $NR^{20}C(O)OR^{21}$ ,  $NR^{20}C(O)R^{21}$ , =O,  $OR^{21}$ ,  $SR^{21}$ ,  $COR^{21}$ ,  $CO_2R^{21}$ ,  $CONR^{20}R^{20a}$ ,  $NHC(O)NR^{20}R^{20a}$ ,  $NHC(S)NR^{20}R^{20a}$ ,  $SO_2NR^{20}R^{20a}$ , and
- 15  $SO_2R^{21}$ ; and  $R^{20}$ ,  $R^{20a}$ , and  $R^{20b}$  are, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl.
- 20 (12) Another embodiment of the invention is a compound of embodiment (1) wherein:
- X is O or S;
- $R^1$  is  $-NR^3R^{3a}$ ,  $-CF_3$ , C<sub>1-4</sub> alkyl substituted with 1-3  $R^4$ ;
- $R^3$  and  $R^{3a}$  are independently selected from the group: H,
- 25 methyl, phenyl and benzyl;
- $R^4$  is, at each occurrence, independently selected from the group: halo, -CN, NO<sub>2</sub>,  $-NR^9R^{9a}$ ,  $NR^9NR^{9a}R^{9b}$ ,  $NR^9C(O)OR^{10}$ ,  $NR^9C(O)R^{10}$ , =O,  $OR^{10}$ ,  $SR^{10}$ ,  $-CF_3$ ,  $COR^{10}$ ,  $CO_2R^{10}$ ,  $CONR^9R^{9a}$ ,  $NHC(O)NR^9R^{9a}$ ,  $NHC(S)NR^9R^{9a}$ ,
- 30  $SO_2NR^9R^{9a}$ ,  $SO_2R^{10}$ , C<sub>3-10</sub> carbocycle substituted with 0-5  $R^{11}$ , and 5-10 membered heterocycle substituted with 0-3  $R^{11}$ ;

5  $R^9$  is, at each occurrence, independently selected from the  
group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;  
 $R^{9a}$  is, at each occurrence, independently selected from the  
group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;  
 $R^{9b}$  is, at each occurrence, independently selected from the  
10 group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;  
 $R^{10}$  is, at each occurrence, independently selected from the  
group: H, C<sub>1-4</sub> alkyl, phenyl, benzyl; and  
 $R^{11}$  is, at each occurrence, independently selected from the  
group consisting of: selected from the group: halo, -  
15 CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl,  $NR^{18}R^{18a}$ ,  
 $NR^{18}NR^{18a}R^{18b}$ ,  $NR^{18}C(O)OR^{17}$ ,  $NR^{18}C(O)R^{17}$ , =O,  $OR^{17}$ ,  
 $SR^{17}$ ,  $COR^{17}$ ,  $CO_2R^{17}$ ,  $CONR^{18}R^{18a}$ ,  $NHC(O)NR^{18}R^{18a}$ ,  
 $NHC(S)NR^{18}R^{18a}$ ,  $SO_2NR^{18}R^{18a}$ ,  $SO_2R^{17}$ , C<sub>3-10</sub> carbocycle  
substituted with 0-5  $R^{19}$ , and 5-10 membered heterocycle  
20 substituted with 0-3  $R^{19}$ .

(13) Another embodiment of the invention is a compound of  
embodiment (1) wherein:

$R^2$  is C<sub>1-4</sub> alkyl substituted with 0-3  $R^7$ , C<sub>2-4</sub> alkenyl  
25 substituted with 0-3  $R^7$ , C<sub>2-4</sub> alkynyl substituted with  
0-3  $R^7$ , -CF<sub>3</sub>, C<sub>3-6</sub> carbocycle substituted with 0-5  $R^8$ ,  
or 3-7 membered heterocycle substituted with 0-5  $R^8$ .

(14) Another embodiment of the invention is a compound of  
30 embodiment (1) wherein:

5     $R^2$  is  $C_{1-4}$  alkyl substituted with 0-3  $R^7$ ,  $C_{2-4}$  alkenyl substituted with 0-3  $R^7$ ,  $C_{2-4}$  alkynyl substituted with 0-3  $R^7$ ,  $-CF_3$ ,  $C_{3-6}$  carbocycle substituted with 0-5  $R^8$ , or 5-7 membered heterocycle substituted with 0-5  $R^8$ .

10    (15) Another embodiment of the invention is a compound of embodiment (1) wherein:

$R^2$  is  $C_{3-6}$  saturated carbocycle substituted with 0-5  $R^8$ , or 5-7 membered saturated heterocycle substituted with 0-5  $R^8$ .

15

(16) Another embodiment of the invention is a compound of embodiment (1) wherein:

$R^2$  is  $C_{5-6}$  partially saturated carbocycle substituted with 0-5  $R^8$ , or 5-7 membered partially saturated heterocycle substituted with 0-5  $R^8$ .

20

(17) Another embodiment of the invention is a compound of embodiment (1) wherein:

25     $R^2$  is phenyl substituted with 0-5  $R^8$ , naphthyl substituted with 0-5  $R^8$  or or 5-6 membered aromatic heterocycle substituted with 0-5  $R^8$ .

(18) Another embodiment of the invention is a compound of embodiment (1) wherein:

30     $R^2$  is phenyl substituted with 0-3  $R^8$ , naphthyl substituted with 0-3  $R^8$  or or 5-6 membered aromatic heterocycle substituted with 0-3  $R^8$ .

5

(19) Another embodiment of the invention is a compound of embodiment (1) wherein:

$R^2$  is C<sub>3-6</sub> carbocycle substituted with 0-5  $R^8$ , or 5-7 membered heterocycle substituted with 0-5  $R^8$ ;

10

$R^8$  is, at each occurrence, independently selected from the group: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, NR<sup>13</sup>R<sup>13a</sup>, NR<sup>13</sup>NR<sup>13a</sup>R<sup>13b</sup>, NR<sup>13</sup>C(O)OR<sup>14</sup>, NR<sup>13</sup>C(O)R<sup>14</sup>, =O, OR<sup>14</sup>, SR<sup>14</sup>, -CF<sub>3</sub>, COR<sup>14</sup>, CO<sub>2</sub>R<sup>14</sup>, CONR<sup>13</sup>R<sup>13a</sup>, NHC(O)NR<sup>13</sup>R<sup>13a</sup>, NHC(S)NR<sup>13</sup>R<sup>13a</sup>, SO<sub>2</sub>NR<sup>13</sup>R<sup>13a</sup>, and SO<sub>2</sub>R<sup>14</sup>, or when two  $R^{8s}$  are attached to two adjacent carbon atoms, the two  $R^{8s}$  may combine to form -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-; and

15

R<sup>13</sup> R<sup>13a</sup>, and R<sup>13b</sup> are, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl; or

20

R<sup>13</sup> and R<sup>13a</sup>, together with the nitrogen atom to which they are attached, form a 5-7 membered heterocycle substituted with 0-3 R<sup>16</sup>.

25

(20) Another embodiment of the invention is a compound of embodiment (1) wherein:

$R^2$  is C<sub>3-6</sub> carbocycle substituted with 0-5  $R^8$ , or 5-7 membered heterocycle substituted with 0-5  $R^8$ ;

30

$R^8$  is, at each occurrence, independently selected from the group: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, NR<sup>13</sup>R<sup>13a</sup>, NR<sup>13</sup>NR<sup>13a</sup>R<sup>13b</sup>, NR<sup>13</sup>C(O)OR<sup>14</sup>, NR<sup>13</sup>C(O)R<sup>14</sup>, =O,

5       OR<sup>14</sup>, SR<sup>14</sup>, -CF<sub>3</sub>, COR<sup>14</sup>, CO<sub>2</sub>R<sup>14</sup>, CONR<sup>13</sup>R<sup>13a</sup>,  
       NHC(O)NR<sup>13</sup>R<sup>13a</sup>, NHC(S)NR<sup>13</sup>R<sup>13a</sup>, SO<sub>2</sub>NR<sup>13</sup>R<sup>13a</sup>, SO<sub>2</sub>R<sup>14</sup>,  
       C<sub>3-10</sub> carbocycle substituted with 0-5 R<sup>15</sup>, and 5-10  
       membered heterocycle substituted with 0-3 R<sup>15</sup>, or when  
       two R<sup>8s</sup> are attached to two adjacent carbon atoms, the  
 10       two R<sup>8s</sup> may combine to form -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-;  
       R<sup>13</sup> R<sup>13a</sup>, and R<sup>13b</sup> are, at each occurrence, independently  
       selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and  
       benzyl; and  
       R<sup>15</sup> is, at each occurrence, independently selected from the  
 15       group consisting of: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub>  
       haloalkyl, NR<sup>20</sup>R<sup>20a</sup>, NR<sup>20b</sup>NR<sup>20</sup>R<sup>20a</sup>, NR<sup>20</sup>C(O)OR<sup>21</sup>,  
       NR<sup>20</sup>C(O)R<sup>21</sup>, =O, OR<sup>21</sup>, SR<sup>21</sup>, COR<sup>21</sup>, CO<sub>2</sub>R<sup>21</sup>, CONR<sup>20</sup>R<sup>20a</sup>,  
       NHC(O)NR<sup>20</sup>R<sup>20a</sup>, NHC(S)NR<sup>20</sup>R<sup>20a</sup>, SO<sub>2</sub>NR<sup>20</sup>R<sup>20a</sup>, and  
       SO<sub>2</sub>R<sup>21</sup>, or when two R<sup>15s</sup> are attached to two adjacent  
 20       carbon atoms, the two R<sup>15s</sup> may combine to form -OCH<sub>2</sub>O-  
       or -OCH<sub>2</sub>CH<sub>2</sub>O-.

25       A more preferred embodiment, is a compound according to  
       any of embodiments (2) to (12) further comprising embodiment  
       (13).

      A more preferred embodiment, is a compound according to  
       any of embodiments (2) to (12) further comprising embodiment  
       (14).

30       A more preferred embodiment, is a compound according to  
       any of embodiments (2) to (12) further comprising embodiment  
       (15).



5 A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment (16).

A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment  
10 (17).

A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment (18).

A more preferred embodiment, is a compound according to  
15 any of embodiments (2) to (12) further comprising embodiment (19).

A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment (20).

20 In a most preferred embodiment, the compounds of formula (I) are selected from:

3-(4-methoxyphenyl)-5-(2-(3,5-dimethoxybenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

25

3-(4-methoxyphenyl)-5-(2-isonicotinoyl  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-nicotinoylhydrazinecarbox  
30 amido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxybenzoyl)hydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one;

35 3-(4-methoxyphenyl)-5-(2-(4-hydroxybenzoyl)hydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one;

5

3-(4-methoxyphenyl)-5-(2-(3-aminobenzoyl)hydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one;

10

3-(4-methoxyphenyl)-5-(2-(4-aminobenzoyl)hydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2-aminobenzoyl)hydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one;

15

3-(4-methoxyphenyl)-5-(2-(4-N,N-dimethylaminobenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-methoxybenzoylhydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one;

20

3-(4-methoxyphenyl)-5-(2-(2-hydroxybenzoyl)hydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one; and

25

3-(4-methoxyphenyl)-5-(2-(3,5-diaminobenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(1-naphthoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

30

3-(4-methoxyphenyl)-5-(2-amido  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-phenylamido  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

35

- 5 3-(4-methoxyphenyl)-5-(2-(4-methylbenzoyl  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 3-(4-methoxyphenyl)-5-(2-(2-naphthoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 10 3-(4-methoxyphenyl)-5-(2-(3-(4-hydroxyphenyl)propionyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 3-(4-methoxyphenyl)-5-(2-(4-methoxybenzoyl)  
15 hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 20 3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 3-(4-methoxyphenyl)-5-(2-(2-thienoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 25 3-(4-methoxyphenyl)-5-(2-(3-methylbenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 3-(4-methoxyphenyl)-5-(2-(3-amino-4-hydroxybenzoyl)  
30 hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 3-(4-methoxyphenyl)-5-(2-(2,5-dichlorobenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 35 3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxybenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

5

3-(4-piperazinyphenyl)-5-(2-(nicotinoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-(4-methylpiperazinyphenyl)-5-(2-(nicotinoyl)  
10 hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-(4-methylpiperazinyphenyl)-5-(2-(isonicotinoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

15 3-(4-piperazinyphenyl)-5-(2-(isonicotinoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one; and

3-(4-piperazinyphenyl)-5-(2-(3,5-dimethoxybenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one; or  
20 a pharmaceutically acceptable salt form thereof, a  
pharmaceutically acceptable prodrug form thereof, an N-oxide  
form thereof, or a stereoisomer thereof.

Another embodiment of the present invention is a  
25 pharmaceutical composition comprising: a pharmaceutically  
acceptable carrier and a therapeutically effective amount of  
a compound of formula (I).

Another embodiment of the present invention is a method  
of treating a proliferative disease associated with CDK  
30 activity comprising: administering to a host in need of  
such treatment a therapeutically effective amount of a  
compound of formula (I), or a pharmaceutically effective  
salt form thereof.

Another embodiment of the present invention is a method  
35 of treating a cell proliferative disease associated with CDK  
activity in a patient, comprising administering to said  
patient a pharmaceutically effective amount of a compound of

5 formula (I), wherein the proliferative diseases is selected from the group consisting of: Alzheimer's disease, viral infections, auto-immune diseases, fungal disease, cancer, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis  
10 glomerulonephritis, neurodegenerative disorders and post-surgical stenosis and restenosis.

Another embodiment of the present invention is a method of treating cancer associated with CDK activity in a patient, comprising administering to said patient a  
15 pharmaceutically effective amount of a compound of formula (I), wherein the cancer is selected from the group consisting of: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix,  
20 thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell  
25 lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and  
30 peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

35 Another embodiment of the present invention is a method of treating a disease associated with apoptosis in a patient, comprising administering to said patient a pharmaceutically effective amount of a compound of formula (I), wherein the disease associated with apoptosis is

5 selected from the group consisting of: cancer, viral  
infections, autoimmune diseases and neurodegenerative  
disorder.

Another embodiment of the present invention is a method  
of inhibiting tumor angiogenesis and metastasis in a  
10 patient, comprising administering to said patient a  
pharmaceutically effective amount of a compound of formula  
(I).

Another embodiment of the present invention is a method  
of treating a disease associated with protein kinase  
15 activity in a patient, comprising administering to said  
patient a pharmaceutically effective amount of a compound of  
formula (I), wherein the protein kinase is selected from the  
group consisting of: e.g. protein kinase C, her2, raf1,  
MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF receptor,  
20 PI3 kinase, weel kinase, Src, and Abl.

Another embodiment of the present invention is a method  
of modulating the level of cellular RNA and DNA synthesis in  
a patient, comprising administering to said patient a CDK  
inhibitory effective amount of a compound of formula (I).

25 Another embodiment of the present invention is a method  
of treating viral infections in a patient, comprising  
administering to said patient a CDK inhibitory effective  
amount of a compound of formula (I), wherein the viral  
infections is selected from the group consisting of HIV,  
30 human papilloma virus, herpesvirus, poxvirus, Epstein-Barr  
virus, Sindbis virus and adenovirus.

Another embodiment of the present invention is a method  
of chemopreventing cancer in a patient, comprising  
administering to said patient a CDK inhibitory effective  
35 amount of a compound of formula (I).

Another embodiment of the present invention is a method  
of inhibiting CDK activity comprising combining an effective  
amount of the compound of formula (I) with a composition  
containing CDK.

5 Another embodiment of the present invention is a method  
of treating cancer associated with CDK activity in a  
patient, comprising administering to said patient a  
pharmaceutically effective amount of a compound of formula  
(I) in combination (administered together or sequentially)  
10 with known anti-cancer treatments such as radiation therapy  
or with cytostatic or cytotoxic agents, such as for example,  
DNA interactive agents, such as cisplatin or doxorubicin;  
topoisomerase II inhibitors, such as etoposide;  
topoisomerase I inhibitors such as CPT-11 or topotecan;  
15 tubulin interacting agents, such as paclitaxel, docetaxel or  
the epothilones; hormonal agents, such as tamoxifen;  
thymidilate synthase inhibitors, such as 5-fluorouracil; and  
anti-metabolites, such as methotrexate.

Another embodiment of the present invention is a method  
20 treating proliferative diseases associated with CDK  
activity, in a patient, comprising administering to said  
patient a pharmaceutically effective amount of a compound of  
formula (I), in combination (administered together or  
sequentially) with known anti-proliferating agents selected  
25 from the group consisting of: , altretamine, busulfan,  
chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine,  
melphalan, thiotepe, cladribine, fluorouracil, floxuridine,  
gemcitabine, thioguanine, pentostatin, methotrexate, 6-  
mercaptapurine, cytarabine, carmustine, lomustine,  
30 streptozotocin, carboplatin, cisplatin, oxaliplatin,  
ipropilatin, tetraplatin, lobaplatin, JM216, JM335,  
fludarabine, aminoglutethimide, flutamide, goserelin,  
leuprolide, megestrol acetate, cyproterone acetate,  
tamoxifen, anastrozole, bicalutamide, dexamethasone,  
35 diethylstilbestrol, prednisone, bleomycin, dactinomycin,  
daunorubicin, doxorubicin, idarubicin, mitoxantrone,  
losoxantrone, mitomycin-c, plicamycin, paclitaxel,  
docetaxel, CPT-11, epothilones , topotecan, irinotecan, 9-  
amino camptothecan, 9-nitro camptothecan, GS-211, etoposide,

5    teniposide, vinblastine, vincristine, vinorelbine,  
      procarbazine, asparaginase, pegaspargase, methotrexate,  
      octreotide, and estramustine, hydroxyurea.

      Another embodiment of the present invention is a method  
of inhibiting CDK1 activity, comprising administering to a  
10   patient in need thereof an effective CDK1 inhibitory amount  
of a compound according to claim 1, or a pharmaceutically  
acceptable salt or prodrug form thereof.

      Another embodiment of the present invention is a method  
of inhibiting CDK2 activity, comprising administering to a  
15   patient in need thereof an effective CDK2 inhibitory amount  
of a compound according to claim 1, or a pharmaceutically  
acceptable salt or prodrug form thereof.

      Another embodiment of the present invention is a method  
of inhibiting CDK3 activity, comprising administering to a  
20   patient in need thereof an effective CDK3 inhibitory amount  
of a compound according to claim 1, or a pharmaceutically  
acceptable salt or prodrug form thereof.

      Another embodiment of the present invention is a method  
of inhibiting CDK4 activity, comprising administering to a  
25   patient in need thereof an effective CDK4 inhibitory amount  
of a compound according to claim 1, or a pharmaceutically  
acceptable salt or prodrug form thereof.

      Another embodiment of the present invention is a method  
of inhibiting CDK5 activity, comprising administering to a  
30   patient in need thereof an effective CDK5 inhibitory amount  
of a compound according to claim 1, or a pharmaceutically  
acceptable salt or prodrug form thereof.

      Another embodiment of the present invention is a method  
of inhibiting CDK6 activity, comprising administering to a  
35   patient in need thereof an effective CDK6 inhibitory amount  
of a compound according to claim 1, or a pharmaceutically  
acceptable salt or prodrug form thereof.

      Another embodiment of the present invention is a method  
of inhibiting CDK7 activity, comprising administering to a



5 patient in need thereof an effective CDK7 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

Another embodiment of the present invention is a method of inhibiting CDK8 activity, comprising administering to a  
10 patient in need thereof an effective CDK8 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

Another embodiment of the present invention is a method of inhibiting CDK9 activity, comprising administering to a  
15 patient in need thereof an effective CDK9 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

It is a further object of the invention to provide a pharmaceutical kit for combination treatment of  
20 proliferative diseases associated with CDK activity, said kit comprising a plurality of separate containers, wherein at least one of said containers contains a compound of formula (I), and at least another of said containers contains one or more compounds selected from the group  
25 consisting of altretamine, busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, thiotepa, cladribine, fluorouracil, floxuridine, gemcitabine, thioguanine, pentostatin, methotrexate, 6-mercaptopurine, cytarabine, carmustine, lomustine,  
30 streptozotocin, carboplatin, cisplatin, oxaliplatin, iproplatin, tetraplatin, lobaplatin, JM216, JM335, fludarabine, aminoglutethimide, flutamide, goserelin, leuprolide, megestrol acetate, cyproterone acetate, tamoxifen, anastrozole, bicalutamide, dexamethasone,  
35 diethylstilbestrol, prednisone, bleomycin, dactinomycin, daunorubicin, doxorubicin, idarubicin, mitoxantrone, losoxantrone, mitomycin-c, plicamycin, paclitaxel, docetaxel, CPT-11, epothilones, topotecan, irinotecan, 9-amino camptothecin, 9-nitro camptothecin, GS-211, etoposide,

5    teniposide, vinblastine, vincristine, vinorelbine,  
procarbazine, asparaginase, pegaspargase, methoxtrexate,  
octreotide, and estramustine, hydroxyurea, and said  
containers optionally contain a pharmaceutical carrier.

10    It is a further object of the invention to provide a  
method of treating a patient having a disorder associated  
with excessive cell proliferation, comprising administering  
to the patient a therapeutically effective amount of a  
compound of formula (I), such that the excessive cell  
proliferation in the patient is reduced.

15    It is appreciated that certain features of the  
invention, which are, for clarity, described in the context  
of separate embodiments, may also be provided in combination  
in a single embodiment. Conversely, various features of  
the invention which are, for brevity, described in the  
20    context of a single embodiment, may also be provided  
separately or in any suitable subcombination.

#### DETAILED DESCRIPTION OF THE INVENTION

25    As used above, and throughout the description of the  
invention, the following terms, unless otherwise indicated,  
shall be understood to have the following meanings:

#### Definitions

30    As used herein, the following terms and expressions  
have the indicated meanings.

35    The term "compounds of the invention", and equivalent  
expressions, are meant to embrace compounds of the invention  
as hereinbefore described i.e. compounds of formula (I),  
which expression includes the prodrugs thereof, N-oxides  
thereof, the pharmaceutically acceptable salts thereof, and  
the solvates thereof, e.g. hydrates, where the context so  
permits. Similarly, reference to intermediates, whether or  
not they themselves are claimed, is meant to embrace their  
salts, and solvates, where the context so permits.

5           The term "derivative" means a chemically modified compound wherein the modification is considered routine by the ordinary skilled chemist, such as an ester or an amide of an acid, protecting groups, such as a benzyl group for an alcohol or thiol, and tert-butoxycarbonyl group for an  
10 amine.

          The term "effective amount" means an amount of a compound/composition according to the present invention effective in producing the desired therapeutic effect.

          The term "amine protecting group" means an easily  
15 removable group which is known in the art to protect an amino group against undesirable reaction during synthetic procedures and to be selectively removable. The use of amine protecting groups is well known in the art for protecting groups against undesirable reactions during a  
20 synthetic procedure and many such protecting groups are known, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Preferred amine protecting groups are acyl, including  
25 formyl; acetyl, chloroacetyl, trichloroacetyl, o-nitrophenylacetyl, o-nitrophenoxyacetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, o-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl and the like, and acyloxy including methoxycarbonyl, 9-  
30 fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, vinylloxycarbonyl, allyloxycarbonyl, t-butyloxycarbonyl (BOC), 1,1-dimethylpropynyloxycarbonyl, benzyloxycarbonyl (CBZ), p-nitrobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, and  
35 the like.

          The term "acid labile amine protecting group" means an amine protecting group as defined above which is readily removed by treatment with acid while remaining relatively

5 stable to other reagents. A preferred acid labile amine protecting group is *tert*-butoxycarbonyl (BOC).

The term "hydrogenation labile amine protecting group" means an amine protecting group as defined above which is readily removed by hydrogenation while remaining relatively  
10 stable to other reagents. A preferred hydrogenation labile amine protecting group is benzyloxycarbonyl (CBZ).

The term "hydrogenation labile acid protecting group" means an acid protecting group as defined above which is readily removed by hydrogenation while remaining relatively  
15 stable to other reagents. A preferred hydrogenation labile acid protecting group is benzyl.

The term "analogue" means a compound which comprises a chemically modified form of a specific compound or class thereof, and which maintains the pharmaceutical and/or  
20 pharmacological activities characteristic of said compound or class.

The term "patient" includes both human and other mammals.

The term "pharmaceutical composition" means a  
25 composition comprising a compound of formula (I) and at least one component selected from the group comprising pharmaceutically acceptable carriers, diluents, adjuvants, excipients, or vehicles, such as preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents,  
30 suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Examples of suspending agents include ethoxylated isostearyl  
35 alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents,

5 for example, parabens, chlorobutanol, phenol, sorbic acid,  
and the like. It may also be desirable to include isotonic  
agents, for example sugars, sodium chloride and the like.  
Prolonged absorption of the injectable pharmaceutical form  
can be brought about by the use of agents delaying  
10 absorption, for example, aluminum monostearate and gelatin.  
Examples of suitable carriers, diluents, solvents or  
vehicles include water, ethanol, polyols, suitable mixtures  
thereof, vegetable oils (such as olive oil) and injectable  
organic esters such as ethyl oleate. Examples of excipients  
15 include lactose, milk sugar, sodium citrate, calcium  
carbonate, dicalcium phosphate phosphate. Examples of  
disintegrating agents include starch, alginic acids and  
certain complex silicates. Examples of lubricants include  
magnesium stearate, sodium lauryl sulphate, talc, as well as  
20 high molecular weight polyethylene glycols.

The term "solvate" means a physical association of a  
compound of this invention with one or more solvent  
molecules. This physical association includes hydrogen  
bonding. In certain instances the solvate will be capable  
25 of isolation, for example when one or more solvent molecules  
are incorporated in the crystal lattice of the crystalline  
solid. "Solvate" encompasses both solution-phase and  
isolable solvates. Exemplary solvates include hydrates,  
ethanolates, methanolates, and the like.

30 The term "alkyl" is intended to include both branched  
and straight-chain saturated aliphatic hydrocarbon groups  
having the specified number of carbon atoms. Examples of  
alkyl include, but are not limited to, methyl, ethyl, n-  
propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and  
35 s-pentyl. In addition, the term is intended to include both  
unsubstituted and substituted alkyl groups, the latter  
referring to alkyl moieties having one or more hydrogen  
substituents replaced by, but not limited to halogen,  
hydroxyl, carbonyl, alkoxy, ester, ether, cyano, phosphoryl,

5 amino, imino, amido, sulfhydryl, alkythio, thioester, sulfonyl, nitro, heterocyclo, aryl or heteroaryl. It will also be understood by those skilled in the art that the substituted moieties themselves can be substituted as well when appropriate.

10 The term "alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 10 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 8 carbon atoms in the chain; and more preferably about 2 to  
15 about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. Exemplary alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl, and  
20 decenyl.

The term "alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 10 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 8  
25 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. Exemplary alkynyl groups include ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl and decynyl.  
30

The terms "halo" or "halogen" as used herein refer to fluoro, chloro, bromo and iodo. The term "aryl" is intended to mean an aromatic moiety containing the specified number of carbon atoms, such as, but not limited to phenyl, indanyl  
35 or naphthyl. The terms "cycloalkyl" and "bicycloalkyl" are intended to mean any stable ring system, which may be saturated or partially unsaturated. Examples of such include, but are not limited to, cyclopropyl, cyclopentyl,

5 cyclohexyl, norbornyl, bicyclo[2.2.2]nonane, adamantly, or tetrahydronaphthyl (tetralin).

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any  
10 of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl,;  
[3.3.0]bicyclooctane, [4.3.0]bicyclononane,  
15 [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5- to 7- membered  
20 monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any  
25 bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable  
30 structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the  
35 heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than

5 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting  
10 of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-  
15 quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl,  
20 chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl,  
25 isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl., oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl,  
35 pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl,



5 quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxaliny, quinucidiny, carboliny, tetrahydrofurany, tetrahydroisoquinoliny, tetrahydroquinoliny, 6H-1,2,5-thiadiaziny, 1,2,3-thiadiazoly, 1,2,4-thiadiazoly, 1,2,5-thiadiazoly, 1,3,4-thiadiazoly, thianthreny, thiazoly, 10 thieny, thienothiazoly, thienooxazoly, thienoimidazoly, thiopheny, triaziny, 1,2,3-triazoly, 1,2,4-triazoly, 1,2,5-triazoly, 1,3,4-triazoly, xantheny. Preferred heterocycles include, but are not limited to, pyridiny, furany, thieny, pyrroly, pyrazoly, imidazoly, indoly, 15 benzimidazoly, 1H-indazoly, oxazolidiny, benzotriazoly, benzisoxazoly, oxindoly, benzoxazoliny, or isatinoy. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, "pharmaceutically acceptable salts" 20 refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic 25 salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such 30 conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, 35 citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-

5    acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic,  
ethane disulfonic, oxalic, isethionic, and the like.

10       The pharmaceutically acceptable salts of the present  
invention can be synthesized from the parent compound which  
contains a basic or acidic moiety by conventional chemical  
15    methods. Generally, such salts can be prepared by reacting  
the free acid or base forms of these compounds with a  
stoichiometric amount of the appropriate base or acid in  
water or in an organic solvent, or in a mixture of the two;  
generally, nonaqueous media like ether, ethyl acetate,  
15    ethanol, isopropanol, or acetonitrile are preferred. Lists  
of suitable salts are found in Remington's Pharmaceutical  
Sciences, 18th ed., Mack Publishing Company, Easton, PA,  
1990, p. 1445, the disclosure of which is hereby  
incorporated by reference.

20       The phrase "pharmaceutically acceptable" is employed  
herein to refer to those compounds, materials, compositions,  
and/or dosage forms which are, within the scope of sound  
medical judgment, suitable for use in contact with the  
tissues of human beings and animals without excessive  
25    toxicity, irritation, allergic response, or other problem or  
complication commensurate with a reasonable benefit/risk  
ratio.

30       The term "Pharmaceutically acceptable prodrugs" as used  
herein means those prodrugs of the compounds useful  
30    according to the present invention which are, within the  
scope of sound medical judgment, suitable for use in contact  
with the tissues of humans and lower animals with undue  
toxicity, irritation, allergic response, and the like,  
commensurate with a reasonable benefit/risk ratio, and  
35    effective for their intended use, as well as the  
zwitterionic forms, where possible, of the compounds of the  
invention.

5       The term "Prodrugs", as the term is used herein, are intended to include any covalently bonded carriers which release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Since prodrugs are known to enhance numerous  
10 desirable qualities of pharmaceuticals (i.e., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same,  
15 and compositions containing the same. Prodrugs of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. The transformation *in vivo*  
20 may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality. Prodrugs include compounds of the present invention wherein a hydroxy, amino,  
25 or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Functional groups which may be rapidly transformed, by metabolic  
30 cleavage, *in vivo* form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to such groups as alkanoyl (such as acetyl, propionyl, butyryl, and the like), unsubstituted and substituted aroyl (such as benzoyl and  
35 substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds

5 useful according to this invention are cleaved in vivo, the  
compounds bearing such groups act as pro-drugs. The  
compounds bearing the metabolically cleavable groups have  
the advantage that they may exhibit improved bioavailability  
as a result of enhanced solubility and/or rate of absorption  
10 conferred upon the parent compound by virtue of the presence  
of the metabolically cleavable group. A thorough discussion  
of prodrugs is provided in the following: Design of  
Prodrugs, H. Bundgaard, ed., Elsevier, 1985; Methods in  
Enzymology, K. Widder et al, Ed., Academic Press, 42, p.309-  
15 396, 1985; A Textbook of Drug Design and Development,  
Krogsgaard-Larsen and H. Bundgaard, ed., Chapter 5; "Design  
and Applications of Prodrugs" p.113-191, 1991; Advanced Drug  
Delivery Reviews, H. Bundgaard, 8, p.1-38, 1992; Journal of  
Pharmaceutical Sciences, 77, p. 285, 1988; Chem. Pharm.  
20 Bull., N. Nakeya et al, 32, p. 692, 1984; Pro-drugs as  
Novel Delivery Systems, T. Higuchi and V. Stella, Vol. 14 of  
the A.C.S. Symposium Series, and Bioreversible Carriers in  
Drug Design, Edward B. Roche, ed., American Pharmaceutical  
Association and Pergamon Press, 1987, which are incorporated  
25 herein by reference.

"Substituted" is intended to indicate that one or more  
hydrogens on the atom indicated in the expression using  
"substituted" is replaced with a selection from the  
indicated group(s), provided that the indicated atom's  
30 normal valency is not exceeded, and that the substitution  
results in a stable compound. When a substituent is keto  
(i.e., =O) group, then 2 hydrogens on the atom are replaced.

The term "Treating" refers to:

(i) preventing a disease, disorder or condition from  
35 occurring in an animal which may be predisposed to the  
disease, disorder and/or condition but has not yet  
been diagnosed as having it;

- 5 (ii) inhibiting the disease, disorder or condition, i.e.,  
arresting its development; and  
(iii) relieving the disease, disorder or condition, i.e.,  
causing regression of the disease, disorder and/or  
condition.

10 Preparation of Compounds of the Invention

It will be apparent to those skilled in the art that  
certain compounds of formula (I) can exhibit isomerism, for  
example geometrical isomerism, e.g., E or Z isomerism, and  
optical isomerism, e.g., R or S configurations. Geometrical  
15 isomers include the cis and trans forms of compounds of the  
invention having alkenyl moieties. It is well known in the  
art how to prepare optically active forms, such as by  
resolution of racemic forms or by synthesis from optically  
active starting materials. All chiral, diastereomeric,  
20 racemic forms and all geometric isomeric forms of a  
structure are intended, unless the specific stereochemistry  
or isomer form is specifically indicated.

Such isomers can be separated from their mixtures, by  
the application or adaptation of known methods, for example  
25 chromatographic techniques and recrystallization techniques;  
or they are separately prepared from the appropriate isomers  
of their intermediates, for example by the application or  
adaptation of methods described herein.

The compounds of the present invention are useful in  
30 the form of the free base or acid or in the form of a  
pharmaceutically acceptable salt thereof. All forms are  
within the scope of the invention.

Where the compound of the present invention is  
substituted with a basic moiety, acid addition salts are  
35 formed and are simply a more convenient form for use; and in  
practice, use of the salt form inherently amounts to use of  
the free base form. The acids which can be used to prepare  
the acid addition salts include preferably those which  
produce, when combined with the free base, pharmaceutically

5 acceptable salts, that is, salts whose anions are non-toxic  
to the patient in pharmaceutical doses of the salts, so that  
the beneficial inhibitory effects on CDK inherent in the  
free base are not vitiated by side effects ascribable to the  
anions. Although pharmaceutically acceptable salts of said  
10 basic compounds are preferred, all acid addition salts are  
useful as sources of the free base form even if the  
particular salt, per se, is desired only as an intermediate  
product as, for example, when the salt is formed only for  
purposes of purification, and identification, or when it is  
15 used as intermediate in preparing a pharmaceutically  
acceptable salt by ion exchange procedures.

According to a further feature of the invention, acid  
addition salts of the compounds of this invention are  
prepared by reaction of the free base with the appropriate  
20 acid, by the application or adaptation of known methods.  
For example, the acid addition salts of the compounds of  
this invention are prepared either by dissolving the free  
base in aqueous or aqueous-alcohol solution or other  
suitable solvents containing the appropriate acid and  
25 isolating the salt by evaporating the solution, or by  
reacting the free base and acid in an organic solvent, in  
which case the salt separates directly or can be obtained by  
concentration of the solution.

The compounds of this invention can be regenerated from  
30 their corresponding acid addition salts by the application  
or adaptation of known methods. For example, parent  
compounds of the invention can be regenerated from their  
acid addition salts by treatment with an alkali, e.g.  
aqueous sodium bicarbonate solution or aqueous ammonia  
35 solution.

Where the compound of the invention is substituted with  
an acidic moiety, base addition salts may be formed and are  
simply a more convenient form for use; and in practice, use  
of the salt form inherently amounts to use of the free acid

5 form. The bases which can be used to prepare the base  
addition salts include preferably those which produce, when  
combined with the free acid, pharmaceutically acceptable  
salts, that is, salts whose cations are non-toxic to the  
animal organism in pharmaceutical doses of the salts, so  
10 that the beneficial inhibitory effects on CDK inherent in  
the free acid are not vitiated by side effects ascribable to  
the cations. Pharmaceutically acceptable salts, including  
for example alkali and alkaline earth metal salts, within  
the scope of the invention are those derived from the  
15 following bases: sodium hydride, sodium hydroxide,  
potassium hydroxide, calcium hydroxide, aluminum hydroxide,  
lithium hydroxide, magnesium hydroxide, zinc hydroxide,  
ammonia, ethylenediamine, N-methyl-glucamine, lysine,  
arginine, ornithine, choline, N,N'-dibenzylethylenediamine,  
20 chlorprocaine, diethanolamine, procaine,  
N-benzylphenethylamine, diethylamine, piperazine,  
tris(hydroxymethyl)-aminomethane, tetramethylammonium  
hydroxide, and the like.

Metal salts of compounds of the present invention may  
25 be obtained by contacting a hydride, hydroxide, carbonate or  
similar reactive compound of the chosen metal in an aqueous  
or organic solvent with the free acid form of the compound.  
The aqueous solvent employed may be water or it may be a  
mixture of water with an organic solvent, preferably an  
30 alcohol such as methanol or ethanol, a ketone such as  
acetone, an aliphatic ether such as tetrahydrofuran, or an  
ester such as ethyl acetate. Such reactions are normally  
conducted at ambient temperature but they may, if desired,  
be conducted with heating.

35 Amine salts of compounds of the present invention may  
be obtained by contacting an amine in an aqueous or organic  
solvent with the free acid form of the compound. Suitable  
aqueous solvents include water and mixtures of water with  
alcohols such as methanol or ethanol, ethers such as

5 tetrahydrofuran, nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

The compounds of this invention can be regenerated from their corresponding base addition salts by the application  
10 or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

Pharmaceutically acceptable salts also include  
15 quaternary lower alkyl ammonium salts. The quaternary salts are prepared by the exhaustive alkylation of basic nitrogen atoms in compounds, including nonaromatic and aromatic basic nitrogen atoms, according to the invention, i.e., alkylating the non-bonded pair of electrons of the nitrogen moieties  
20 with an alkylating agent such as methylhalide, particularly methyl iodide, or dimethyl sulfate. Quaternarization results in the nitrogen moiety becoming positively charged and having a negative counter ion associated therewith.

As will be self-evident to those skilled in the art,  
25 some of the compounds of this invention do not form stable salts. However, acid addition salts are more likely to be formed by compounds of this invention having a nitrogen-containing heteroaryl group and/or wherein the compounds contain an amino group as a substituent. Preferable acid  
30 addition salts of the compounds of the invention are those wherein there is not an acid labile group.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for  
35 example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

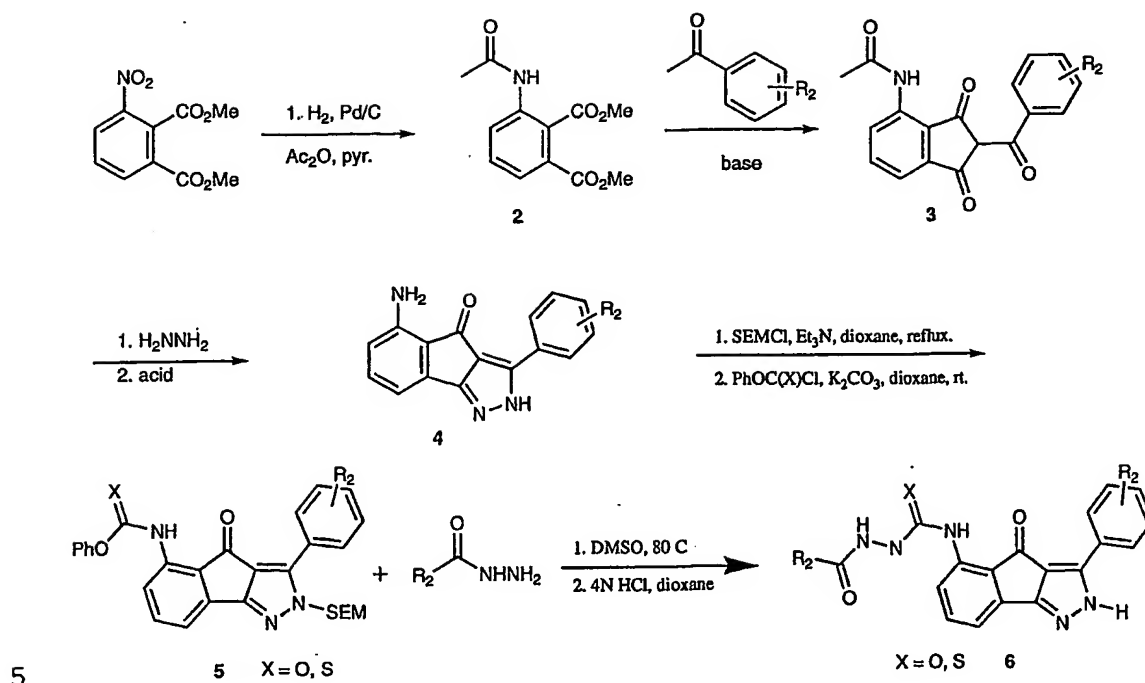


5       Compounds according to the invention, for example,  
starting materials, intermediates or products, are prepared  
as described herein or by the application or adaptation of  
known methods, by which is meant methods used heretofore or  
described in the literature, for example those described by  
10 R. C. Larock in Comprehensive Organic Transformations, VCH  
publishers, 1989.

      In the reactions described hereinafter it may be  
necessary to protect reactive functional groups, for example  
hydroxy, amino, imino, thio or carboxy groups, where these  
15 are desired in the final product, to avoid their unwanted  
participation in the reactions. Conventional protecting  
groups may be used in accordance with standard practice, for  
examples see T.W. Green and P.G.M. Wuts in "Protective Groups  
in Organic Chemistry" John Wiley and Sons, 1991; J. F. W.  
20 McOmie in "Protective Groups in Organic Chemistry" Plenum  
Press, 1973.

      Preferred methods of synthesizing the compounds of the  
invention include, but are not limited to, those methods  
described below. Each of the references cited below are  
25 hereby incorporated herein by reference.

Scheme 1

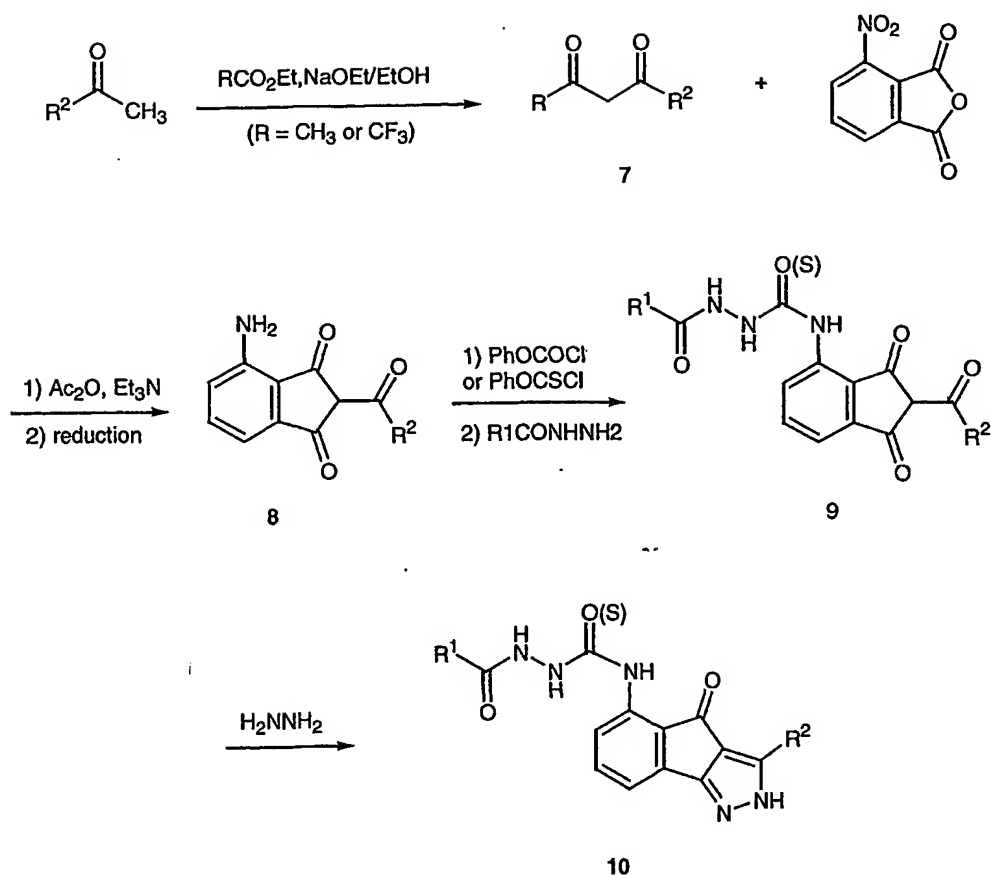


An approach to preparing indeno[1,2-c]pyrazol-4-ones is presented in Scheme 1 and can be used to prepare compounds of the present invention. The nitro group of dimethyl 3-nitrophthalate was reduced to the amine using catalytic hydrogenation. The aniline was acylated using acetic anhydride and pyridine as a base. A mixture of the resulting acetamide 2 and an acetophenone were treated with a strong base in an appropriate solvent at elevated temperature to give the desired triketone 3. Additional means of preparing triketones are known to one skilled in the art as described in Kilgore et al, Industrial and Engineering Chemistry 34:494-497, 1946, the contents of which are hereby incorporated herein by reference. The triketone was treated with hydrazine at elevated temperature in an appropriate solvent to give the indeno[1,2-c]pyrazol-4-one ring system. Additional means of preparing indeno[1,2-c]pyrazol-4-ones are known to one skilled in the art as described in Lemke et al., J. Heterocyclic Chem. 19:1335-1340, 1982; Mosher and

5 Soeder, J. Heterocyclic Chem. 8:855-59, 1971; Hrniciar and  
Svanygova Collect. Czech. Chem. Commun. 59:2734-40, 1994 the  
contents of which are hereby incorporated herein by  
reference. The amide was deacylated by heating with a strong  
acid in an appropriate solvent to give aniline 4. Treating  
10 the intermediate 5-aminoindeno[1,2-c]pyrazol-4-one (4) with  
2-(trimethylsilyl) ethoxymethylmethyl chloride (SEMCl) and a  
suitable base in an inert solvent under reflux gives the SEM  
protected intermediate. The aniline is converted to the  
carbamate 5 using methods known to those skilled in the art.  
15 This intermediate is reacted with carbazates in DMSO at  
elevated temperatures and then the SEM group is removed by  
treating with acid in a polar protic solvent to give the  
desired acylsemicarbazide-containing indenopyrazole analogs  
6.

20

Scheme 2



5

Another method for preparing the triketones 3 of Scheme 1 employs the condensation of a 1,3-diketone 7 with 3-nitrophthalic anhydride as described in Rotberg and Oshkaya, Zh. Organ. Khim. 8:84-87, 1972; Zh. Organ. Khim. 9:2548-2550, 1973, the contents of which are hereby incorporated herein by reference. The 1,3-diketones, when not commercially available can be readily prepared by one skilled in the art by the acetylation or trifluoroacetylation of the requisite methyl ketone, R<sup>1</sup>COCH<sub>3</sub>. Reduction of the nitro derivative to the aniline 8 can be accomplished in a variety of ways including catalytic hydrogenation, treatment with zinc or iron under acidic conditions, or treatment with other reducing agents such as sodium dithionite or stannous chloride. Acetylation of the aniline 8 provides the triketones 3.

20

5           Alternatively, the indeno[1,2-c]pyrazol-4-ones of this invention can be prepared as shown in Scheme 2. Exposure of aniline 8 to phenyl chloroformate or phenyl chlorothionoformate in the presence of base, followed by treatment of the intermediate with the appropriate carbazate, provides either trione 9, a hydrazone of 9, or mixtures of 9 and its hydrazone. When 9 or its hydrazone is allowed to react with hydrazine as described above the pyrazoles 10 are obtained.

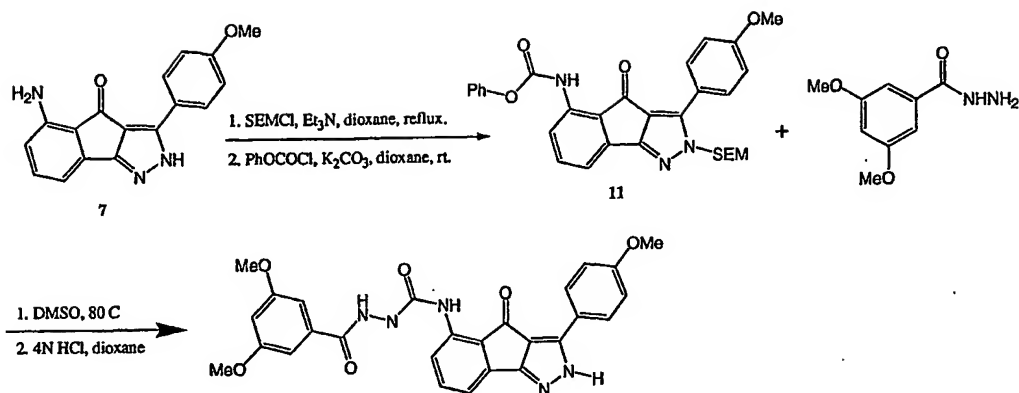
Other features of the invention will become apparent during the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

#### Examples

Abbreviations used in the Examples are defined as follows: "°C" for degrees Celsius, "CIMS" for chemical ionization mass spectroscopy, "eq" for equivalent or equivalents, "g" for gram or grams, "h" for hour or hours, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "mmol" for millimolar, "M" for molar, "min" for minute or minutes, "p-TsOH" for para-toluenesulphonic acid, "DMF" for dimethylformamide, and "TFA" for trifluoroacetic acid.

#### Example I

30           Preparation of 3-(4-methoxyphenyl)-5-(2-(3,5-dimethoxybenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one



5

Step 1. Synthesis of 11 from 7.

The synthesis for the starting aniline is this example  
 10 is described in WO 9954308 and is incorporated herein by  
 reference. A suspension of aniline 7 (0.5 g, 1.7 mmol) in  
 dioxane (10 mL) was treated with triethylamine (0.48 mL, 3.4  
 mmol) in one portion at room temperature. Then 2-  
 (trimethylsilyl) ethyloxy chloride (SEMCl) (0.48 mL, 2.6  
 15 mmol) was added in one portion and the mixture heated to  
 reflux for 2 h. The reaction was cooled, diluted with EtOAc  
 (20 mL) washed with water (10 mL), dried (MgSO<sub>4</sub>) and the  
 solvent removed at reduced pressure. The residue was taken  
 up in benzene (3 mL), applied to a plug of silica gel (10 g)  
 20 and eluted with EtOAc/Hexane (1:3) until all the yellow  
 color was washed from the silica gel plug. The solvent was  
 evaporated and the residue taken on to the next step. This  
 material was dissolved in dioxane (10 mL) and treated with  
 K<sub>2</sub>CO<sub>3</sub> (0.36 g, 2.6 mmol) in one portion. Then  
 25 phenylchloroformate (0.27 mL, 2.23 mmol) was added in one  
 portion and the reaction heated to 50 C for 2 h. The  
 reaction was cooled and the solvent removed at reduced  
 pressure. The residue was recrystallized from EtOH to give a

- 5 yellow solid (0.4 g, 43%). mp °C; CIMS m/e calculated for  $C_{30}H_{32}N_3O_5Si$ : 542.2111, found: 542.2101.

Step 2. Synthesis of Ex. I from 11.

- Compound 11 (0.015 g, 0.03 mmol) in DMSO (0.2 mL) was  
10 treated with 3,5-dimethoxyphenylcarbазate (0.008 g, 0.06  
mmol) in one portion and heated to 80 C for 30 minutes. The  
solvent was removed at reduced pressure heating to 65 C. The  
residue was dissolved in EtOH (0.5 mL) and treated with 4N  
HCl/dioxane (0.4 mL). The mixture was heated to 80 C for 20  
15 minutes and then cooled. The desired product was filtered  
and air dried (0.008g, 62%). mp >300 °C; CIMS m/e calculated  
for  $C_{27}H_{24}N_5O_6(M+H^+)$ : 514.1727, found: 514.1777.

#### Example II

- 20 Preparation of 3-(4-methoxyphenyl)-5-(2-  
isonicotinoylhydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

- Prepared in a similar fashion as described for example  
I using 4-pyridylcarbазate as the starting material. mp 248  
°C; CIMS m/e calculated for  $C_{24}H_{19}N_6O_4(M+H^+)$ : 455.1468,  
25 found: 455.1400.

#### Example III

- Preparation of 3-(4-methoxyphenyl)-5-(2-  
nictinoylhydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

- 30 Prepared in a similar fashion as described for example  
I using 3-pyridylcarbазate as the starting material. mp 227  
°C; CIMS m/e calc'd for  $C_{24}H_{19}N_6O_4(M+H^+)$ : 455.1468, found:  
455.1487.

- 35 Example IV

5      Preparation of 3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxy  
         benzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

         Prepared in a similar fashion as described for example  
I using 3,4-dihydroxyphenyl carbazate as the starting  
material. mp >300 °C; CIMS m/e calc'd for C<sub>25</sub>H<sub>20</sub>N<sub>5</sub>O<sub>6</sub> (M+H<sup>+</sup>):  
10    486.1414, found: 486.1497.

Example V

Preparation of 3-(4-methoxyphenyl)-5-(2-(4-hydroxy  
         benzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

15      Prepared in a similar fashion as described for example  
I using 4-hydroxyphenyl carbazate as the starting material.  
mp 283 °C; CIMS m/e calc'd for C<sub>25</sub>H<sub>20</sub>N<sub>5</sub>O<sub>5</sub> (M+H<sup>+</sup>): 470.1464,  
found: 470.1544.

Example VI

20      Preparation of 3-(4-methoxyphenyl)-5-(2-(3-  
         aminobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

         Prepared in a similar fashion as described for example  
I using 3-aminophenyl carbazate as the starting material. mp  
25    250 °C; CIMS m/e calc'd for C<sub>25</sub>H<sub>21</sub>N<sub>6</sub>O<sub>4</sub> (M+H<sup>+</sup>): 469.1624,  
found: 469.1513.

Example VII

30      Preparation of 3-(4-methoxyphenyl)-5-(2-(4-  
         aminobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

         Prepared in a similar fashion as described for example  
I using 4-aminophenyl carbazate as the starting material. mp  
247 °C; CIMS m/e calc'd for C<sub>25</sub>H<sub>21</sub>N<sub>6</sub>O<sub>4</sub> (M+H<sup>+</sup>): 469.1624,  
found: 469.1528.

35

Example VIII



5           Preparation of 3-(4-methoxyphenyl)-5-(2-(2-aminobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one  
Prepared in a similar fashion as described for example I using 2-aminophenyl carbazate as the starting material. mp 257 °C; CIMS m/e calc'd for C<sub>25</sub>H<sub>21</sub>N<sub>6</sub>O<sub>4</sub> (M+H<sup>+</sup>): 469.1624,  
10 found: 469.1548;

Example IX

Preparation of 3-(4-methoxyphenyl)-5-(2-(4-N,N-dimethylamino benzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one  
15       Prepared in a similar fashion as described for example I using 4-N,N-dimethylaminophenyl carbazate as the starting material. mp 259 °C; CIMS m/e calc'd for C<sub>27</sub>H<sub>25</sub>N<sub>6</sub>O<sub>4</sub> (M+H<sup>+</sup>): 497.1937, found: 497.1876.

20           Example X

Preparation of 3-(4-methoxyphenyl)-5-(2-methoxybenzoyl hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one  
Prepared in a similar fashion as described for example I using 2-methoxyphenyl carbazate as the starting material.  
25 mp 269 °C; CIMS m/e calc'd for C<sub>26</sub>H<sub>22</sub>N<sub>5</sub>O<sub>5</sub> (M+H<sup>+</sup>): 484.1621, found: 484.1613.

Example XI

Preparation of 3-(4-methoxyphenyl)-5-(2-(2-hydroxy benzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one  
30       Prepared in a similar fashion as described for example I using 2-hydroxyphenyl carbazate as the starting material. mp 280 °C; CIMS m/e calc'd for C<sub>25</sub>H<sub>20</sub>N<sub>5</sub>O<sub>5</sub> (M+H<sup>+</sup>): 470.1464, found: 470.1419.

35

Example XII

5    Preparation of 3-(4-methoxyphenyl)-5-(2-(3,5-diaminobenzoyl)  
          hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3,5-diaminophenyl carbazate as the starting material. mp >300 °C; CIMS m/e calc'd for C<sub>25</sub>H<sub>22</sub>N<sub>7</sub>O<sub>4</sub>(M+H<sup>+</sup>):

10    484.1733, found: 484.1776.

Example XIII

Preparation of 3-(4-methoxyphenyl)-5-(2-(1-naphthoyl)  
          hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

15    Prepared in a similar fashion as described for example I using 1-naphthhydrazide as the starting material. CIMS m/e calc'd for C<sub>29</sub>H<sub>22</sub>N<sub>5</sub>O<sub>4</sub>(M+H<sup>+</sup>): 504.1672, found: 504.1706.

Example XIV

20    Preparation of 3-(4-methoxyphenyl)-5-(2-amido  
          hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using semicarbazide as the starting material. CIMS m/e calc'd for C<sub>19</sub>H<sub>17</sub>N<sub>6</sub>O<sub>4</sub>(M+H<sup>+</sup>): 393.1311, found: 393.1333.

25

Example XV

Preparation of 3-(4-methoxyphenyl)-5-(2-phenylamido  
          hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

30    Prepared in a similar fashion as described for example I using 4-phenylsemicarbazide as the starting material. CIMS m/e calc'd for C<sub>25</sub>H<sub>21</sub>N<sub>6</sub>O<sub>4</sub>(M+H<sup>+</sup>): 469.1624, found: 469.1681.

Example XVI

5           Preparation of 3-(4-methoxyphenyl)-5-(2-(4-methylbenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 4-methylphenyl carbazate as the starting material.

10 CIMS m/e calc'd for  $C_{26}H_{22}N_5O_4(M+H^+)$ : 468.1672, found: 468.1688.

Example XVII

15           Preparation of 3-(4-methoxyphenyl)-5-(2-(2-naphthoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 2-naphthhadrazide as the starting material. CIMS m/e calc'd for  $C_{29}H_{22}N_5O_4(M+H^+)$ : 504.1672, found: 504.1710.

20           Example XVIII

Preparation of 3-(4-methoxyphenyl)-5-(2-(3-(4-hydroxyphenyl)propionyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 4-hydroxyhydrocinamic acid hydrazide as the starting material. CIMS m/e calc'd for  $C_{27}H_{24}N_5O_5(M+H^+)$ : 498.1777, found: 498.1711.

Example XIX

30           Preparation of 3-(4-methoxyphenyl)-5-(2-(4-methoxybenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 4-methoxybenzhydrazide as the starting material.

35 CIMS m/e calc'd for  $C_{26}H_{22}N_5O_5(M+H^+)$ : 484.1621, found: 484.1600.

5

Example XX

Preparation of 3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3-nitrobenzhydrazide as the starting material. CIMS m/e calc'd for  $C_{25}H_{19}N_6O_6 (M+H^+)$ : 499.1366, found: 499.1304.

Example XXI

Preparation of 3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3,4,5-trimethoxybenzhydrazide as the starting material. CIMS m/e calc'd for  $C_{28}H_{26}N_5O_7 (M+H^+)$ : 544.1832, found: 544.1812.

20

Example XXII

Preparation of 3-(4-methoxyphenyl)-5-(2-(2-thienoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 2-thenoic hydrazide as the starting material. CIMS m/e calc'd for  $C_{23}H_{18}N_5O_4S (M+H^+)$ : 460.1080, found: 460.1012.

Example XXIII

Preparation of 3-(4-methoxyphenyl)-5-(2-(3-methylbenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3-methylbenzoic acid hydrazide as the starting material. CIMS m/e calc'd for  $C_{26}H_{22}N_5O_4 (M+H^+)$ : 468.1672, found: 468.1640.

5

Example XXV

Preparation of 3-(4-methoxyphenyl)-5-(2-(2,5-dichlorobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 2,5-dichlorobenzoic acid hydrazide as the starting material. CIMS m/e calc'd for  $C_{25}H_{18}N_5O_4Cl_2 (M+H^+)$ : 522.0736, found: 522.0777.

Example XXVI

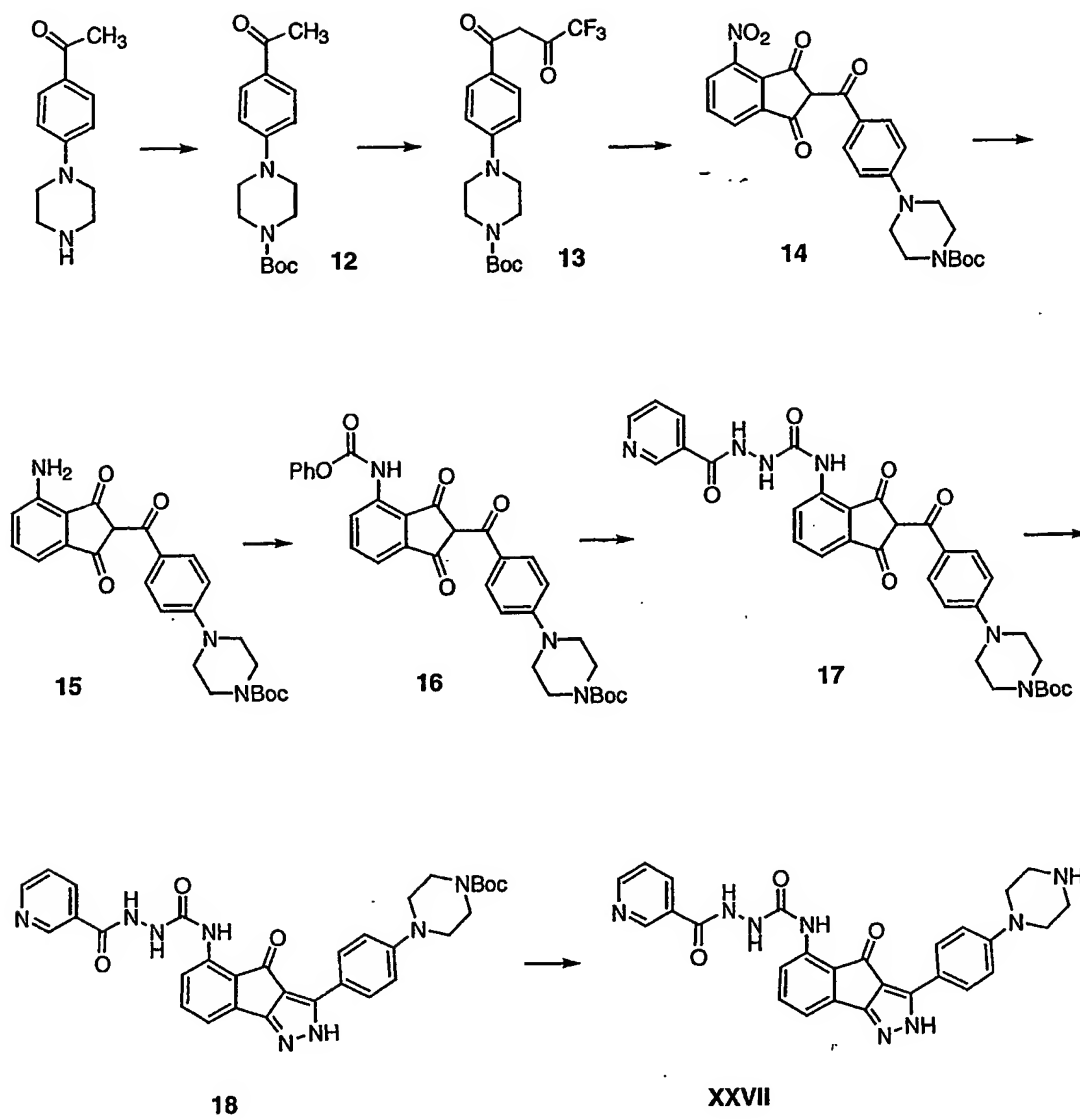
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Preparation of 3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxybenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3,4-dihydroxybenzoic acid hydrazide as the starting material. CIMS m/e calc'd for  $C_{25}H_{20}N_5O_6 (M+H^+)$ : 486.1414, found: 486.1445.

Example XXVII

Preparation of 3-(4-piperazinyphenyl)-5-(2-(nicotinoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one



### Step 1. Preparation of 12

To a suspension of 139g (680 mmol) of 4-piperazinoacetophenone in 700mL of tetrahydrofuran at 25°C was added slowly over 20 min. a solution of 157g (720 mmol) of di-tert-butyl dicarbonate in 300mL of tetrahydrofuran. The resulting mixture was refluxed for 15h. After cooling the mixture was filtered, and the filtrate was concentrated under vacuum to provide an off-white solid. This crude product was recrystallized from diethyl ether/hexane to

5 afford 192g of the 12 as a white solid. NMR (CDCl<sub>3</sub>)  $\delta$  7.89 (d, 2 H, J = 9 Hz), 6.87 (d, 2 H, J = 9 Hz), 3.59 (m, 4 H), 3.33 (m, 4 H), 2.53 (s, 3 H), 1.49 (s, 9 H).

Step 2. Preparation of 13 from 12

10 To a solution of 192g (630 mmol) of 12 and 90mL (750 mmol) of ethyl trifluoroacetate in 1000 mL of tetrahydrofuran at 25 °C was added slowly over 15 min. 280 mL (750 mmol) of 21% sodium ethoxide in ethanol, and the resulting solution then was stirred at 25°C for 16 h. The  
15 reaction mixture was diluted with 500mL of water, and to this mixture was added 45mL of acetic acid. The resulting precipitate was recovered by filtration. The solids were washed with diethyl ether/hexane and dried to furnish 236g of 13 as an orange solid. NMR (CDCl<sub>3</sub>)  $\delta$  7.87 (d, 2 H, J = 9  
20 Hz), 6.87 (d, 2 H, J = 9 Hz), 6.45 (s, 1 H), 3.60 (m, 4 H), 3.41 (m, 4 H), 1.48 (s, 9 H).

Step 3. Preparation of 14 from 13

A suspension of 117g (610 mmol) of 3-nitrophthalic  
25 anhydride in 560mL of acetic anhydride was heated until the mixture became homogeneous, and the solution then was allowed to cool to room temperature. To this solution was added 236g (590 mmol) of 13. The resulting mixture was cooled to 0°C, and 165mL (1200 mmol) of triethylamine was  
30 added slowly over 10 min. The mixture was allowed to warm to 25°C, was stirred at 25°C for 1h, and then was heated to 65°C for 0.5h. After cooling to room temperature, the reaction mixture was poured into a well-stirred solution of 1200mL of 1.0 N hydrochloric acid and 2000mL of ethanol. The  
35 resulting precipitate was recovered by filtration, washed with ethanol, and dried to provide 140g of 14 as an orange solid. NMR (acetone-d<sub>6</sub>)  $\delta$  8.34 (d, 2H, J = 9 Hz), 8.05 (m, 3H), 7.07 (d, 2H, J = 9 Hz), 3.59 (br s, 8H), 1.48 (s, 9H).

5

## Step 4. Preparation of 15 from 14

To a solution of 12.00g (25 mmol) of 14 in 500mL of ethanol and 50mL of conc. ammonium hydroxide at 25°C was added 500mL of water, followed by 15.3g (88 mmol) of sodium dithionite. The resulting mixture was stirred at 25°C for 16h. The reaction mixture was filtered, and the filtrate was reduced to ~1/2 the original volume under vacuum. This solution was adjusted to pH 3 employing hydrochloric acid and then extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over anhyd. sodium sulfate, filtered, and concentrated. The resulting solids were recrystallized from ethanol/water to provide 8.40g of 15 as a green solid. NMR (DMSO- $d_6$ )  $\delta$  8.20 (d, 2H, J = 9 Hz), 7.44 (t, 1H, J = 8 Hz), 7.02 (d, 2H, J = 9 Hz), 6.96 (d, 1H, J = 8 Hz), 6.91 (d, 1H, J = 8 Hz), 6.70 (br s, 2H), 3.46 (br s, 8H), 1.43 (s, 9H).

## Step 5. Preparation of 16 from 15

To a mixture of 7.05g (15.6 mmol) of 15, 8.67g (63 mmol) of potassium carbonate, 250mL of acetone at 25°C was added 2.40mL of phenyl chloroformate, and the resulting mixture was stirred at 25°C for 20h. The mixture was diluted with 500mL of water, adjusted to pH 3 employing hydrochloric acid, and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over anhyd. sodium sulfate, filtered, and dried. The crude product was recrystallized from ethanol/water to afford 6.32g of 16 as a dark yellow solid. Mass Spec: m/e = 582 (M-H)<sup>-</sup>.

## Step 6. Preparation of 18 from 16



5       A solution of 0.57g (1.0 mmol) of 16 and 0.41g (3.0 mmol) of nicotinic acid hydrazide in 20mL of DMSO was stirred at 90°C for 2h. After cooling the solvent was removed under high vacuum to afford crude 17.

10       A solution of the crude 17, 0.10mL (2.0 mmol) of hydrazine hydrate, and 0.014g (0.2 mmol) of hydrazine hydrochloride in 20mL of ethanol was refluxed for 20h. While still at reflux the reaction mixture was diluted by dropwise addition of 10mL of water at a rate such that the refluxing of the solution was continuous. The mixture was allowed to  
15 cool to room temperature, and the resulting precipitate was recovered by filtration, washed with 95% ethanol, and dried to provide 0.25g of 18 as a yellow solid.

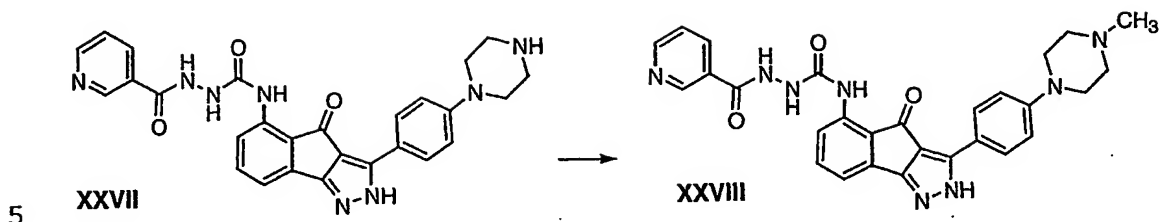
#### Step 7. Preparation of XXVII from 18

20       A solution of 0.25g (0.4 mmol) of 18 in 10mL of trifluoroacetic acid was stirred at 25°C for 2h. The excess trifluoroacetic acid was removed under vacuum, and the residue was dissolved in 20mL of hot ethanol. After cooling, the resulting precipitate was recovered by filtration under  
25 nitrogen and then dried under vacuum to afford 0.16g of the desired product as its trifluoroacetate salt. mp 232 °C; CIMS m/e calc'd for C<sub>27</sub>H<sub>25</sub>N<sub>8</sub>O<sub>3</sub>(M+H<sup>+</sup>): 509.2050, found: 509.2060.

30

#### Example XXVIII

Preparation of 3-(4-(4-methylpiperazinyl)phenyl)-5-(2-(nicotinoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one



To a solution of 0.16g (0.26 mmol) of XXVII in 15mL of methanol and 5mL of water at 25°C was added sequentially  
 10 0.77g (9.5 mmol) of 37% aqueous formaldehyde, 0.32g (5.1 mmol) of sodium cyanoborohydride, and 3 drop of acetic acid. The resulting solution was stirred for 16h at 25°C. The solution was made acidic (pH<1) with conc. hydrochloric acid and was stirred for 20 min. until gas evolution ceased. The  
 15 solution then was made basic (pH.13) with 50% aqueous sodium hydroxide solution. The mixture was stirred for 20 min, and then was adjusted to pH 9 with hydrochloric acid. The resulting precipitate was recovered by filtration, washed with 95% ethanol, and dried under vacuum. The yellow solid  
 20 thus obtained was dissolved in 2mL of trifluoroacetic acid, and the solution was diluted with 10mL of hot anhydrous ethanol. Upon cooling a precipitate formed. This solid was recovered by filtration and dried under vacuum to afford 0.08g of the desired product as its trifluoroacetate salt.  
 25 mp 238 °C; CIMS m/e calc'd for C<sub>28</sub>H<sub>27</sub>N<sub>8</sub>O<sub>3</sub> (M+H<sup>+</sup>): 523.2206, found: 523.2210.

#### Example XXIX

Preparation of 3-(4-(4-methylpiperazinyl)phenyl)-5-(2-  
 30 (isonicotinoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-  
one

- 5        Prepared from example XXX in a similar fashion as described for example XXVIII. mp 240 °C; CIMS m/e calc'd for  $C_{28}H_{27}N_8O_3 (M+H^+)$ : 523.2206, found: 523.2208.

Example XXX

- 10        Preparation of 3-(4-piperazinylphenyl)-5-(2-(isonicotinoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

- Prepared in a similar fashion as described for example XXVII using isonicotinic acid hydrazide as the starting material. mp 232 °C; CIMS m/e calc'd for  $C_{27}H_{25}N_8O_3 (M+H^+)$ : 509.2050, found: 509.2065.
- 15

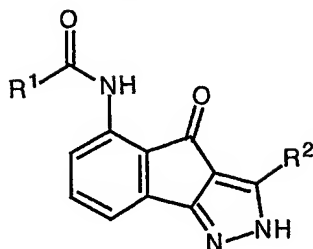
Example XXXI

- Preparation of 3-(4-piperazinylphenyl)-5-(2-(3,5-dimethoxybenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one
- 20

- Prepared in a similar fashion as described for example XXVII using 3,5-dimethoxybenzoic hydrazide as the starting material. mp >300 °C; CIMS m/e calc'd for  $C_{30}H_{30}N_7O_5 (M+H^+)$ : 568.2309, found: 568.2316.
- 25

5

Table 1



Example #	R <sup>1</sup> -C(O)N(R <sup>5</sup> )NH-	R <sup>2</sup>	mass (M <sup>+</sup> H)	mp (°C)
I	3,5-dimethoxy C <sub>6</sub> H <sub>3</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	514	>300
II	4-pyridylC(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	455	248
III	3-pyridylC(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	455	227
IV	3,4-dihydroxy- C <sub>6</sub> H <sub>3</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	486	>300
V	4-hydroxy- C <sub>6</sub> H <sub>4</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	470	283
VI	3-amino-C <sub>6</sub> H <sub>4</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	469	250
VII	4-amino-C <sub>6</sub> H <sub>4</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	469	247
VIII	2-amino-C <sub>6</sub> H <sub>4</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	469	257
IX	4-N,N-dimethylamino- C <sub>6</sub> H <sub>4</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	497	259
X	2-MeO-C <sub>6</sub> H <sub>4</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	484	269
XI	2-OH-C <sub>6</sub> H <sub>4</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	470	280
XII	3,5-di-NH <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> C (O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	484	>300
XIII	1-naphthylC(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	504	
XIV	H <sub>2</sub> NC(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	393	

XV	$C_6H_4HNC(O)NHNH-$	4-MeOC <sub>6</sub> H <sub>4</sub> -	469	
XVI	4-Me-C <sub>6</sub> H <sub>4</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	468	
XVII	2-naphthylC(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	504	
XVIII	4-OH- $C_6H_4CH_2CH_2C(O)NHNH-$	4-MeOC <sub>6</sub> H <sub>4</sub> -	498	
XIX	4-MeO-C <sub>6</sub> H <sub>4</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	484	
XX	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	499	
XXI	3,4,5-tri-MeO- $C_6H_2C(O)NHNH-$	4-MeOC <sub>6</sub> H <sub>4</sub> -	544	
XXII	2-thienylC(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	460	
XXIII	3-Me-C <sub>6</sub> H <sub>4</sub> C(O)NHNH-	4-MeOC <sub>6</sub> H <sub>4</sub> -	468	
XXIV	3-NH <sub>2</sub> -4-OH- $C_6H_3C(O)NHNH-$	4-MeOC <sub>6</sub> H <sub>4</sub> -	485	
XXV	2,5-di-Cl- $C_6H_3C(O)NHNH-$	4-MeOC <sub>6</sub> H <sub>4</sub> -	522	
XXVI	3,4-di-OH- $C_6H_3C(O)NHNH-$	4-MeOC <sub>6</sub> H <sub>4</sub> -	486	
XXVII	3-pyridylC(O)NHNH-	4-piperazinyl C <sub>6</sub> H <sub>4</sub> -	509	232
XXVIII	3-pyridylC(O)NHNH-	4-(4-Me- piperazinyl) C <sub>6</sub> H <sub>4</sub> -	523	238
XXIX	4-pyridylC(O)NHNH-	4-(4-Me- piperazinyl) C <sub>6</sub> H <sub>4</sub> -	523	240
XXX	4-pyridylC(O)NHNH-	4-piperazinyl C <sub>6</sub> H <sub>4</sub> -	509	232
XXXI	3,5-di-MeO- $C_6H_3C(O)NHNH-$	4-piperazinyl C <sub>6</sub> H <sub>4</sub> -	568	>300

5

The compounds useful according to the invention optionally are supplied as salts. Those salts which are pharmaceutically acceptable are of particular interest since they are useful in administering the foregoing compounds for medical purposes. Salts which are not pharmaceutically acceptable are useful in manufacturing processes, for isolation and purification purposes, and in some instances, for use in separating stereoisomeric forms of the compounds of this invention. The latter is particularly true of amine salts prepared from optically active amines.

Where the compound useful according to the invention contains a carboxy group, or a sufficiently acidic bioisostere, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form.

Also, where the compound useful according to the invention contains a basic group, or a sufficiently basic bioisostere, acid addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form.

The foregoing compounds useful according to the invention may also be mixed another therapeutic compound to form pharmaceutical compositions (with or without diluent or carrier) which, when administered, provide simultaneous administration of a combination of active ingredients resulting in the combination therapy of the invention.

While it is possible for the compounds useful according to the invention to be administered alone it is preferably to present them as pharmaceutical compositions. The pharmaceutical compositions, both for veterinary and for human use, useful according to the present invention comprise at least one compound of the invention, as above

5 defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients.

In certain preferred embodiments, active ingredients necessary in combination therapy may be combined in a single pharmaceutical composition for simultaneous administration.

10 The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the active compound, the particular mode of administration and the provisions to be observed in pharmaceutical  
15 practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be  
20 used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol,  
25 polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the oily phase may comprise merely an emulsifier  
30 (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include  
35 both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the emulsifying wax, and the way together with the oil and fat make up the emulsifying ointment base which forms the oily dispersed phase of a cream formulation. Emulgents and emulsion stabilizers

5    suitable for use in the formulation of the present invention  
include Tween® 60, Span® 80, cetostearyl alcohol, benzyl  
alcohol, myristyl alcohol, glyceryl mono-stearate and sodium  
lauryl sulfate.

10    If desired, the aqueous phase of the cream base may  
include, for example, a least 30% w/w of a polyhydric  
alcohol, i.e. an alcohol having two or more hydroxyl groups  
such as propylene glycol, butane 1,3-diol, mannitol,  
sorbitol, glycerol and polyethylene glycol (including PEG  
15    400) and mixtures thereof. The topical formulations may  
desirably include a compound which enhances absorption or  
penetration of the active ingredient through the skin or  
other affected areas. Examples of such dermal penetration  
enhancers include dimethyl sulphoxide and related analogue.

20    The choice of suitable oils or fats for the formulation  
is based on achieving the desired cosmetic properties. Thus  
the cream should preferably be a non-greasy, non-staining  
and washable product with suitable consistency to avoid  
leakage from tubes or other containers. Straight or  
branched chain, mono- or dibasic alkyl esters such as di-  
25    isopropyl myristate, decyl oleate, isopropyl palmitate,  
butyl stearate, 2-ethylhexyl palmitate or a blend of  
branched chain esters known as Crodamol CAP may be used, the  
last three being preferred esters. These may be used alone  
or in combination depending on the properties required.  
30    Alternatively, high melting point lipids such as white soft  
paraffin and/or liquid paraffin or other mineral oils can be  
used. Solid compositions of may also be employed as fillers  
in soft and hard-filled gelatin capsules using such  
excipients as lactose or milk sugar as well as high  
35    molecular weight polyethylene glycols, and the like.

The pharmaceutical compositions can be administered in  
a suitable formulation to humans and animals by topical or  
systemic administration, including oral, inhalational,  
rectal, nasal, buccal, sublingual, vaginal, parenteral



5 (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), intracisternal and intraperitoneal. It will be appreciated that the preferred route may vary with for example the condition of the recipient.

10 The formulations can be prepared in unit dosage form by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are  
15 prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

A tablet may be made by compression or moulding,  
20 optionally with one or more accessory ingredients. Compressed tables may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface  
25 active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compounds moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of  
30 the active ingredient therein.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of the invention.

If desired, and for more effective distribution, the  
35 compounds can be microencapsulated in, or attached to, a slow release or targeted delivery systems such as a biocompatible, biodegradable polymer matrices (e.g. poly(d,l-lactide co-glycolide)), liposomes, and microspheres and subcutaneously or intramuscularly injected by a

5 technique called subcutaneous or intramuscular depot to  
provide continuous slow release of the compound(s) for a  
period of 2 weeks or longer. The compounds may be  
sterilized, for example, by filtration through a bacteria  
retaining filter, or by incorporating sterilizing agents in  
10 the form of sterile solid compositions which can be  
dissolved in sterile water, or some other sterile injectable  
medium immediately before use.

Actual dosage levels of active ingredient in the  
compositions of the invention may be varied so as to obtain  
15 an amount of active ingredient that is effective to obtain a  
desired therapeutic response for a particular composition  
and method of administration. The selected dosage level  
therefore depends upon the desired therapeutic effect, on  
the route of administration, on the desired duration of  
20 treatment and other factors.

Total daily dose of the compounds useful according to  
this invention administered to a host in single or divided  
doses may be in amounts, for example, of from about 0.001 to  
about 100 mg/kg body weight daily and preferably 0.01 to 10  
25 mg/kg/day. Dosage unit compositions may contain such  
amounts of such submultiples thereof as may be used to make  
up the daily dose. It will be understood, however, that the  
specific dose level for any particular patient will depend  
upon a variety of factors including the body weight, general  
30 health, sex, diet, time and route of administration, rates  
of absorption and excretion, combination with other drugs  
and the severity of the particular disease being treated.

The amount of each component administered is determined  
by the attending clinicians taking into consideration the  
35 etiology and severity of the disease, the patient's  
condition and age, the potency of each component and other  
factors.

The formulations may be presented in unit-dose or  
multi-dose containers, for example sealed ampoules and vials

5 with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from  
10 sterile powders, granules and tablets of the kind previously described.

Administration of a compound of the present invention in combination with additional therapeutic agents, may afford an efficacy advantage over the compounds and agents  
15 alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety. The combination of a compound of the present invention with such additional therapeutic agents is preferably a  
20 synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), occurs when the therapeutic effect of the compound and agent when administered in combination is greater than the additive effect of the either the compound or agent when  
25 administered alone. In general, a synergistic effect is most clearly demonstrated at levels that are (therapeutically) sub-optimal for either the compound of the present invention or a known anti-proliferative agent alone, but which are highly efficacious in combination. Synergy can be in terms  
30 of improved inhibitory response without substantial increases in toxicity over individual treatments alone, or some other beneficial effect of the combination compared with the individual components.

The compounds of the invention, their methods or  
35 preparation and their biological activity will appear more clearly from the examination of the following examples which are presented as an illustration only and are not to be considered as limiting the invention in its scope.

5        Procedures for evaluating the biological activity of compounds or compositions according to the invention are carried out as described herein or by the application or adaptation of known procedures, by which is meant procedures used heretofore or as described in the literature.

10

#### UTILITY

##### Inhibition of Kinase/Cyclin Complex Enzymatic Activity

      Several of the compounds disclosed in this invention were assayed for their inhibitory activity against cdk4/D1 and cdk2/E kinase complexes. Briefly, the in vitro assays  
15    employ cell lysates from insect cells expressing either of the kinases and subsequently their corresponding regulatory units. The cdk2/cyclinE is purified from insect cells expressing His-tagged cdk2 and cyclin E. The cdk/cyclin lysate is combined in a microtitre-type plate along with a  
20    kinase compatible buffer, <sup>32</sup>P-labeled ATP at a concentration of 50 mM, a GST-Rb fusion protein and the test compound at varying concentrations. The kinase reaction is allowed to proceed with the radiolabeled ATP, then effectively stopped by the addition of a large excess of EDTA and unlabeled ATP.  
25    The GST-Rb labeled protein is sequestered on a GSH-Sepharose bead suspension, washed, resuspended in scintillant, and the <sup>32</sup>P activity detected in a scintillation counter. The compound concentration which inhibits 50% of the kinase activity was calculated for each compound. A compound was  
30    considered active if its IC<sub>50</sub> was found to be less than 1 μM.

##### Inhibition of HCT 116 Cancer Cell Proliferation

      To test the cellular activity of several compounds disclosed in this invention, we examined the effect of these  
35    compounds on cultured HCT116 cells and determined their effect on cell-cycle progression by the colorimetric

- 5 cytotoxicity test using sulforhodamine B (Skehan et al. J. Natl. Cancer Inst. 82:1107-12, 1990). Briefly, HCT116 cells are cultured in the presence of test compounds at increasing concentrations. At selected time points, groups of cells are fixed with trichloroacetic acid and stained with
- 10 sulforhodamine B (SRB). Unbound dye was removed by washing and protein-bound dye was extracted for determination of optical density. A compound was considered active if its IC<sub>50</sub> was found to be less than 10  $\mu$ M.

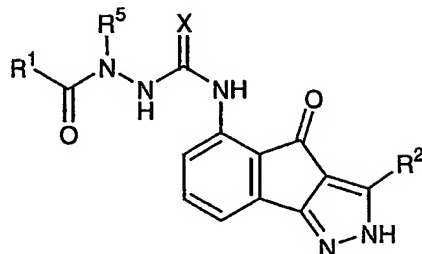
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CLAIMS

What is claimed is:

1. A compound of formula (I):

10



X is O or S;

R<sup>1</sup> is -NR<sup>3</sup>R<sup>3a</sup>, -CF<sub>3</sub>, C<sub>1-4</sub> alkyl substituted with 1-3 R<sup>4</sup>, C<sub>5-10</sub> alkyl substituted with 0-3 R<sup>4</sup>, C<sub>2-C10</sub> alkenyl

15

substituted with 0-3 R<sup>4</sup>, C<sub>2-C10</sub> alkynyl substituted with 0-3 R<sup>4</sup>, C<sub>3-C10</sub> carbocycle substituted with 0-5 R<sup>6</sup>, or 5-10 membered heterocycle substituted with 0-3 R<sup>6</sup>;

provided that if R<sup>1</sup> is phenyl or benzyl, then R<sup>1</sup> is substituted with 1-5 R<sup>6</sup>;

20 R<sup>2</sup> is H, C<sub>1-10</sub> alkyl substituted with 0-3 R<sup>7</sup>, C<sub>2-10</sub> alkenyl substituted with 0-3 R<sup>7</sup>, C<sub>2-10</sub> alkynyl substituted with 0-3 R<sup>7</sup>, -CF<sub>3</sub>, C<sub>3-10</sub> carbocycle substituted with 0-5 R<sup>8</sup>, or 3-10 membered heterocycle substituted with 0-5 R<sup>8</sup>;

R<sup>3</sup> and R<sup>3a</sup> are independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;

25

R<sup>4</sup> and R<sup>7</sup> are, at each occurrence, independently selected from the group: halo, -CN, NO<sub>2</sub>, -NR<sup>9</sup>R<sup>9a</sup>, NR<sup>9</sup>NR<sup>9a</sup>R<sup>9b</sup>, NR<sup>9</sup>C(O)OR<sup>10</sup>, NR<sup>9</sup>C(O)R<sup>10</sup>, =O, OR<sup>10</sup>, SR<sup>10</sup>, -CF<sub>3</sub>, COR<sup>10</sup>,

5 CO<sub>2</sub>R<sup>10</sup>, CONR<sup>9</sup>R<sup>9a</sup>, NHC(O)NR<sup>9</sup>R<sup>9a</sup>, NHC(S)NR<sup>9</sup>R<sup>9a</sup>,  
SO<sub>2</sub>NR<sup>9</sup>R<sup>9a</sup>, SO<sub>2</sub>R<sup>10</sup>, C<sub>3</sub>-10 carbocycle substituted with  
0-5 R<sup>11</sup>, and 5-10 membered heterocycle substituted with  
0-3 R<sup>11</sup>;

R<sup>5</sup> is selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1</sub>-4  
10 alkyl, phenyl and benzyl;

R<sup>6</sup> and R<sup>8</sup> are, at each occurrence, independently selected  
from the group: halo, -CN, NO<sub>2</sub>, C<sub>1</sub>-4 alkyl, C<sub>1</sub>-4  
haloalkyl, NR<sup>13</sup>R<sup>13a</sup>, NR<sup>13</sup>NR<sup>13a</sup>R<sup>13b</sup>, NR<sup>13</sup>C(O)OR<sup>14</sup>,  
NR<sup>13</sup>C(O)R<sup>14</sup>, =O, OR<sup>14</sup>, SR<sup>14</sup>, -CF<sub>3</sub>, COR<sup>14</sup>, CO<sub>2</sub>R<sup>14</sup>,  
15 CONR<sup>13</sup>R<sup>13a</sup>, NHC(O)NR<sup>13</sup>R<sup>13a</sup>, NHC(S)NR<sup>13</sup>R<sup>13a</sup>,  
SO<sub>2</sub>NR<sup>13</sup>R<sup>13a</sup>, SO<sub>2</sub>R<sup>14</sup>, C<sub>3</sub>-10 carbocycle substituted with  
0-5 R<sup>15</sup>, and 5-10 membered heterocycle substituted with  
0-3 R<sup>15</sup>, or when two R<sup>6s</sup> or R<sup>8s</sup> are attached to two  
adjacent carbon atoms, the two R<sup>6s</sup> or R<sup>8s</sup> may combine  
20 to form -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-;

R<sup>9</sup> is, at each occurrence, independently selected from the  
group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1</sub>-4 alkyl, phenyl and  
benzyl;

R<sup>9b</sup> is, at each occurrence, independently selected from the  
25 group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1</sub>-4 alkyl, phenyl and  
benzyl; or

R<sup>9</sup> and R<sup>9a</sup>, together with the nitrogen atom to which they  
are attached, form a heterocycle substituted with 0-3  
R<sup>16</sup>;

30 R<sup>9a</sup> is selected from the group: H, C<sub>1</sub>-4 alkyl, phenyl and  
benzyl;

5 R<sup>10</sup>, R<sup>14</sup>, R<sup>17</sup> are, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl, benzyl;

R<sup>11</sup> is, at each occurrence, independently selected from the group: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, NR<sup>18</sup>R<sup>18a</sup>, NR<sup>18</sup>NR<sup>18a</sup>R<sup>18b</sup>, NR<sup>18</sup>C(O)OR<sup>17</sup>, NR<sup>18</sup>C(O)R<sup>17</sup>, =O, OR<sup>17</sup>, SR<sup>17</sup>, COR<sup>17</sup>, CO<sub>2</sub>R<sup>17</sup>, CONR<sup>18</sup>R<sup>18a</sup>, NHC(O)NR<sup>18</sup>R<sup>18a</sup>, NHC(S)NR<sup>18</sup>R<sup>18a</sup>, SO<sub>2</sub>NR<sup>18</sup>R<sup>18a</sup>, SO<sub>2</sub>R<sup>17</sup>, C<sub>3-10</sub> carbocycle substituted with 0-5 R<sup>19</sup>, and 5-10 membered heterocycle substituted with 0-3 R<sup>19</sup>;

10

R<sup>13</sup> is is, at each occurrence, independently selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and benzyl;

15

R<sup>13a</sup> is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl; or

R<sup>13</sup> and R<sup>13a</sup>, together with the nitrogen atom to which they are attached, form a heterocycle substituted with 0-3 R<sup>16</sup>;

20

R<sup>13b</sup> is, at each occurrence, independently selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and benzyl;

25 R<sup>15</sup>, R<sup>16</sup> and R<sup>19</sup> are, at each occurrence, independently selected from the group: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, NR<sup>20</sup>R<sup>20a</sup>, NR<sup>20b</sup>NR<sup>20</sup>R<sup>20a</sup>, NR<sup>20</sup>C(O)OR<sup>21</sup>, NR<sup>20</sup>C(O)R<sup>21</sup>, =O, OR<sup>21</sup>, SR<sup>21</sup>, COR<sup>21</sup>, CO<sub>2</sub>R<sup>21</sup>, CONR<sup>20</sup>R<sup>20a</sup>, NHC(O)NR<sup>20</sup>R<sup>20a</sup>, NHC(S)NR<sup>20</sup>R<sup>20a</sup>, SO<sub>2</sub>NR<sup>20</sup>R<sup>20a</sup>, SO<sub>2</sub>R<sup>21</sup>, or

30 when two R<sup>15</sup>s, R<sup>16</sup>s or R<sup>19</sup>s are attached to two adjacent



- 5 carbon atoms, the two R<sup>15</sup>s R<sup>16</sup>s or R<sup>19</sup>s may combine to form -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-;
- R<sup>18</sup> is, at each occurrence, independently selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and benzyl;
- 10 R<sup>18a</sup> is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl; or
- R<sup>18</sup> and R<sup>18a</sup>, together with the nitrogen atom to which they are attached, form a heterocycle substituted with 0-3 R<sup>19</sup>;
- 15 R<sup>18b</sup> is, at each occurrence, independently selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and benzyl; or
- R<sup>20</sup> is, at each occurrence, independently selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and
- 20 benzyl;
- R<sup>20a</sup> is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;
- R<sup>20b</sup> is, at each occurrence, independently selected from the group: H, -C(O)R<sup>12</sup>, -C(O)OR<sup>12</sup>, C<sub>1-4</sub> alkyl, phenyl and
- 25 benzyl; and
- R<sup>12</sup> and R<sup>21</sup> are, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl, benzyl; or a pharmaceutically acceptable salt form thereof, a pharmaceutically acceptable prodrug form thereof, an N-
- 30 oxide form thereof, or a stereoisomer thereof.

2. A compound according to claim 1 wherein:

X is O or S;

5  $R^1$  is  $-NR^3R^{3a}$ ,  $-CF_3$ , C1-C4 alkyl substituted with 1-3  $R^4$ , C2-C4 alkenyl substituted with 0-3  $R^4$ , C2-C4 alkynyl substituted with 0-3  $R^4$ , C3-C10 carbocycle substituted with 0-5  $R^6$ , or 5-10 membered heterocycle substituted with 0-3  $R^6$ .

10

3. A compound according to claim 1 wherein:

X is O or S;

$R^1$  is  $-NR^3R^{3a}$ ,  $-CF_3$ , C1-C4 alkyl substituted with 1-3  $R^4$ ,

C2-C4 alkenyl substituted with 0-3  $R^4$ , C2-C4 alkynyl

15 substituted with 0-3  $R^4$ , C3-C6 carbocycle substituted

with 0-5  $R^6$ , or 5-7 membered heterocycle substituted

with 0-3  $R^6$ .

4. A compound according to claim 1 wherein:

20  $R^1$  is C3-C6 saturated carbocycle substituted with 0-5  $R^6$ , or

5-7 membered saturated heterocycle substituted with 0-3  $R^6$ .

5. A compound according to claim 1 wherein:

25  $R^1$  is C5-C6 partially saturated carbocycle substituted with

0-5  $R^6$ , or 5-7 membered partially saturated heterocycle substituted with 0-3  $R^6$ .

6. A compound according to claim 1 wherein:

30  $R^1$  is phenyl substituted with 1-5  $R^6$ , naphthyl substituted

with 0-5  $R^6$ , or 5-6 membered aromatic heterocycle substituted with 0-3  $R^6$ .

5

7. A compound according to claim 1 wherein:

$R^1$  is phenyl substituted with 1-3  $R^6$ , naphthyl substituted with 0-3  $R^6$ , or 5-6 membered aromatic heterocycle substituted with 0-3  $R^6$ .

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8. A compound according to claim 1 wherein:

$R^1$  is  $C_3$ - $C_{10}$  carbocycle substituted with 0-5  $R^6$ , or 5-10 membered heterocycle substituted with 0-3  $R^6$ ;

$R^6$  is, at each occurrence, independently selected from the group: halo, -CN,  $NO_2$ ,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $NR^{13}R^{13a}$ ,  $NR^{13}NR^{13a}R^{13b}$ ,  $NR^{13}C(O)OR^{14}$ ,  $NR^{13}C(O)R^{14}$ , =O,  $OR^{14}$ ,  $SR^{14}$ , -CF<sub>3</sub>,  $COR^{14}$ ,  $CO_2R^{14}$ ,  $CONR^{13}R^{13a}$ ,  $NHC(O)NR^{13}R^{13a}$ ,  $NHC(S)NR^{13}R^{13a}$ ,  $SO_2NR^{13}R^{13a}$ , and  $SO_2R^{14}$ , or when two  $R^{6s}$  are attached to two adjacent carbon atoms, the two  $R^{6s}$  may combine to form -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-.

20

9. A compound according to claim 1 wherein:

$R^6$  is, at each occurrence, independently selected from the group: halo, -CN,  $NO_2$ ,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $NR^{13}R^{13a}$ ,  $NR^{13}NR^{13a}R^{13b}$ ,  $NR^{13}C(O)OR^{14}$ ,  $NR^{13}C(O)R^{14}$ , =O,  $OR^{14}$ ,  $SR^{14}$ , -CF<sub>3</sub>,  $COR^{14}$ ,  $CO_2R^{14}$ ,  $CONR^{13}R^{13a}$ ,  $NHC(O)NR^{13}R^{13a}$ ,  $NHC(S)NR^{13}R^{13a}$ ,  $SO_2NR^{13}R^{13a}$ , and  $SO_2R^{14}$ , or when two  $R^{6s}$  are attached to two adjacent carbon atoms, the two  $R^{6s}$  may combine to form -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-;

30

5 R<sup>13</sup>, R<sup>13a</sup> and R<sup>13b</sup> are, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl; and

R<sup>14</sup> is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl, and benzyl.

10

10. A compound according to claim 1 wherein:

R<sup>6</sup> is independently at each occurrence selected from the group: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, NR<sup>13</sup>R<sup>13a</sup>, NR<sup>13</sup>C(O)OR<sup>14</sup>, NR<sup>13</sup>C(O)R<sup>14</sup>, OR<sup>14</sup>, SR<sup>14</sup>, -CF<sub>3</sub>,  
15 COR<sup>14</sup>, CO<sub>2</sub>R<sup>14</sup>, CONR<sup>13</sup>R<sup>13a</sup>, NHC(S)NR<sup>13</sup>R<sup>13a</sup>, SO<sub>2</sub>NR<sup>13</sup>R<sup>13a</sup>, and SO<sub>2</sub>R<sup>14</sup>;

R<sup>13</sup>, R<sup>13a</sup> and R<sup>13b</sup> are each independently selected from the group: H or methyl; and

R<sup>14</sup> is independently selected from the group: H, methyl,  
20 phenyl, and benzyl.

11. A compound according to claim 1 wherein:

X is O or S;

R<sup>1</sup> is -NR<sup>3</sup>R<sup>3a</sup>, -CF<sub>3</sub>, C<sub>1-4</sub> alkyl substituted with 1-3 R<sup>4</sup>;

25 R<sup>4</sup> is, at each occurrence, independently selected from the group: halo, -CN, NO<sub>2</sub>, -NR<sup>9</sup>R<sup>9a</sup>, NR<sup>9</sup>NR<sup>9a</sup>R<sup>9b</sup>, NR<sup>9</sup>C(O)OR<sup>10</sup>, NR<sup>9</sup>C(O)R<sup>10</sup>, =O, OR<sup>10</sup>, SR<sup>10</sup>, -CF<sub>3</sub>, COR<sup>10</sup>, CO<sub>2</sub>R<sup>10</sup>, CONR<sup>9</sup>R<sup>9a</sup>, NHC(O)NR<sup>9</sup>R<sup>9a</sup>, NHC(S)NR<sup>9</sup>R<sup>9a</sup>, SO<sub>2</sub>NR<sup>9</sup>R<sup>9a</sup>, and SO<sub>2</sub>R<sup>10</sup>;

30 R<sup>9</sup> is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;

- 5  $R^{9a}$  is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;
- $R^{9b}$  is, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl; or
- $R^9$  and  $R^{9a}$ , together with the nitrogen atom to which they  
 10 are attached, form a 5-7 membered heterocycle substituted with 0-3  $R^{16}$ ;
- $R^{16}$  is, at each occurrence, independently selected from the group consisting of: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl,  $NR^{20}R^{20a}$ ,  $NR^{20b}NR^{20}R^{20a}$ ,  $NR^{20}C(O)OR^{21}$ ,  
 15  $NR^{20}C(O)R^{21}$ , =O,  $OR^{21}$ ,  $SR^{21}$ ,  $COR^{21}$ ,  $CO_2R^{21}$ ,  $CONR^{20}R^{20a}$ ,  $NHC(O)NR^{20}R^{20a}$ ,  $NHC(S)NR^{20}R^{20a}$ ,  $SO_2NR^{20}R^{20a}$ , and  $SO_2R^{21}$ ; and
- $R^{20}$ ,  $R^{20a}$ , and  $R^{20b}$  are, at each occurrence, independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and  
 20 benzyl.

12. A compound according to claim 1 wherein:
- X is O or S;
- $R^1$  is  $-NR^3R^{3a}$ ,  $-CF_3$ , C<sub>1-4</sub> alkyl substituted with 1-3  $R^4$ ;
- 25  $R^3$  and  $R^{3a}$  are independently selected from the group: H, methyl, phenyl and benzyl;
- $R^4$  is, at each occurrence, independently selected from the group: halo, -CN, NO<sub>2</sub>,  $-NR^9R^{9a}$ ,  $NR^9NR^{9a}R^{9b}$ ,  
 $NR^9C(O)OR^{10}$ ,  $NR^9C(O)R^{10}$ , =O,  $OR^{10}$ ,  $SR^{10}$ ,  $-CF_3$ ,  $COR^{10}$ ,  
 30  $CO_2R^{10}$ ,  $CONR^9R^{9a}$ ,  $NHC(O)NR^9R^{9a}$ ,  $NHC(S)NR^9R^{9a}$ ,  $SO_2NR^9R^{9a}$ ,  $SO_2R^{10}$ , C<sub>3-10</sub> carbocycle substituted with

5        0-5 R<sup>11</sup>, and 5-10 membered heterocycle substituted with  
          0-3 R<sup>11</sup>;

R<sup>9</sup> is, at each occurrence, independently selected from the  
          group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;

10       R<sup>9a</sup> is, at each occurrence, independently selected from the  
          group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;

R<sup>9b</sup> is, at each occurrence, independently selected from the  
          group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;

R<sup>10</sup> is, at each occurrence, independently selected from the  
          group: H, C<sub>1-4</sub> alkyl, phenyl, benzyl; and

15       R<sup>11</sup> is, at each occurrence, independently selected from the  
          group consisting of: selected from the group: halo, -  
          CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, NR<sup>18</sup>R<sup>18a</sup>,  
          NR<sup>18</sup>NR<sup>18a</sup>R<sup>18b</sup>, NR<sup>18</sup>C(O)OR<sup>17</sup>, NR<sup>18</sup>C(O)R<sup>17</sup>, =O, OR<sup>17</sup>,  
          SR<sup>17</sup>, COR<sup>17</sup>, CO<sub>2</sub>R<sup>17</sup>, CONR<sup>18</sup>R<sup>18a</sup>, NHC(O)NR<sup>18</sup>R<sup>18a</sup>,  
          20       NHC(S)NR<sup>18</sup>R<sup>18a</sup>, SO<sub>2</sub>NR<sup>18</sup>R<sup>18a</sup>, SO<sub>2</sub>R<sup>17</sup>, C<sub>3-10</sub> carbocycle  
          substituted with 0-5 R<sup>19</sup>, and 5-10 membered heterocycle  
          substituted with 0-3 R<sup>19</sup>.

13. A compound according to claim 1 wherein:

25       R<sup>2</sup> is C<sub>1-4</sub> alkyl substituted with 0-3 R<sup>7</sup>, C<sub>2-4</sub> alkenyl  
          substituted with 0-3 R<sup>7</sup>, C<sub>2-4</sub> alkynyl substituted with  
          0-3 R<sup>7</sup>, -CF<sub>3</sub>, C<sub>3-6</sub> carbocycle substituted with 0-5 R<sup>8</sup>,  
          or 3-7 membered heterocycle substituted with 0-5 R<sup>8</sup>.

30       14. A compound according to claim 1 wherein:

- 5     $R^2$  is  $C_{1-4}$  alkyl substituted with 0-3  $R^7$ ,  $C_{2-4}$  alkenyl substituted with 0-3  $R^7$ ,  $C_{2-4}$  alkynyl substituted with 0-3  $R^7$ ,  $-CF_3$ ,  $C_{3-6}$  carbocycle substituted with 0-5  $R^8$ , or 5-7 membered heterocycle substituted with 0-5  $R^8$ .
- 10   15. A compound according to claim 1 wherein:  
 $R^2$  is  $C_{3-6}$  saturated carbocycle substituted with 0-5  $R^8$ , or 5-7 membered saturated heterocycle substituted with 0-5  $R^8$ .
- 15   16. A compound according to claim 1 wherein:  
 $R^2$  is  $C_{5-6}$  partially saturated carbocycle substituted with 0-5  $R^8$ , or 5-7 membered partially saturated heterocycle substituted with 0-5  $R^8$ .
- 20   17. A compound according to claim 1 wherein:  
 $R^2$  is phenyl substituted with 0-5  $R^8$ , naphthyl substituted with 0-5  $R^8$  or or 5-6 membered aromatic heterocycle substituted with 0-5  $R^8$ .
- 25   18. A compound according to claim 1 wherein:  
 $R^2$  is phenyl substituted with 0-3  $R^8$ , naphthyl substituted with 0-3  $R^8$  or or 5-6 membered aromatic heterocycle substituted with 0-3  $R^8$ .
- 30   19. A compound according to claim 1 wherein:

5  $R^2$  is C<sub>3-6</sub> carbocycle substituted with 0-5  $R^8$ , or 5-7  
 membered heterocycle substituted with 0-5  $R^8$ ;

$R^8$  is, at each occurrence, independently selected from the  
 group: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl,  
 10 NR<sup>13</sup>R<sup>13a</sup>, NR<sup>13</sup>NR<sup>13a</sup>R<sup>13b</sup>, NR<sup>13</sup>C(O)OR<sup>14</sup>, NR<sup>13</sup>C(O)R<sup>14</sup>, =O,  
 OR<sup>14</sup>, SR<sup>14</sup>, -CF<sub>3</sub>, COR<sup>14</sup>, CO<sub>2</sub>R<sup>14</sup>, CONR<sup>13</sup>R<sup>13a</sup>,  
 NHC(O)NR<sup>13</sup>R<sup>13a</sup>, NHC(S)NR<sup>13</sup>R<sup>13a</sup>, SO<sub>2</sub>NR<sup>13</sup>R<sup>13a</sup>, and  
 SO<sub>2</sub>R<sup>14</sup>, or when two  $R^{8s}$  are attached to two adjacent  
 carbon atoms, the two  $R^{8s}$  may combine to form -OCH<sub>2</sub>O-  
 15 or -OCH<sub>2</sub>CH<sub>2</sub>O-; and

R<sup>13</sup> R<sup>13a</sup>, and R<sup>13b</sup> are, at each occurrence,  
 independently selected from the group: H, C<sub>1-4</sub> alkyl,  
 phenyl and benzyl; or

R<sup>13</sup> and R<sup>13a</sup>, together with the nitrogen atom to which they  
 20 are attached, form a 5-7 membered heterocycle  
 substituted with 0-3  $R^{16}$ .

20. A compound according to claim 1 wherein:

$R^2$  is C<sub>3-6</sub> carbocycle substituted with 0-5  $R^8$ , or 5-7  
 25 membered heterocycle substituted with 0-5  $R^8$ ;

$R^8$  is, at each occurrence, independently selected from the  
 group: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl,  
 NR<sup>13</sup>R<sup>13a</sup>, NR<sup>13</sup>NR<sup>13a</sup>R<sup>13b</sup>, NR<sup>13</sup>C(O)OR<sup>14</sup>, NR<sup>13</sup>C(O)R<sup>14</sup>, =O,  
 OR<sup>14</sup>, SR<sup>14</sup>, -CF<sub>3</sub>, COR<sup>14</sup>, CO<sub>2</sub>R<sup>14</sup>, CONR<sup>13</sup>R<sup>13a</sup>,  
 30 NHC(O)NR<sup>13</sup>R<sup>13a</sup>, NHC(S)NR<sup>13</sup>R<sup>13a</sup>, SO<sub>2</sub>NR<sup>13</sup>R<sup>13a</sup>, SO<sub>2</sub>R<sup>14</sup>,  
 C<sub>3-10</sub> carbocycle substituted with 0-5  $R^{15}$ , and 5-10



- 5        membered heterocycle substituted with 0-3 R<sup>15</sup>, or when  
       two R<sup>8s</sup> are attached to two adjacent carbon atoms, the  
       two R<sup>8s</sup> may combine to form -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-;
- R<sup>13</sup> R<sup>13a</sup>, and R<sup>13b</sup> are, at each occurrence, independently  
       selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and  
 10        benzyl; and
- R<sup>15</sup> is, at each occurrence, independently selected from the  
       group consisting of: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub>  
       haloalkyl, NR<sup>20</sup>R<sup>20a</sup>, NR<sup>20b</sup>NR<sup>20</sup>R<sup>20a</sup>, NR<sup>20</sup>C(O)OR<sup>21</sup>,  
       NR<sup>20</sup>C(O)R<sup>21</sup>, =O, OR<sup>21</sup>, SR<sup>21</sup>, COR<sup>21</sup>, CO<sub>2</sub>R<sup>21</sup>, CONR<sup>20</sup>R<sup>20a</sup>,  
 15        NHC(O)NR<sup>20</sup>R<sup>20a</sup>, NHC(S)NR<sup>20</sup>R<sup>20a</sup>, SO<sub>2</sub>NR<sup>20</sup>R<sup>20a</sup>, and  
       SO<sub>2</sub>R<sup>21</sup>, or when two R<sup>15s</sup> are attached to two adjacent  
       carbon atoms, the two R<sup>15s</sup> may combine to form -OCH<sub>2</sub>O-  
       or -OCH<sub>2</sub>CH<sub>2</sub>O-.
- 20    21. A compound according to claim 1 wherein:  
       X is O or S;  
       R<sup>1</sup> is -NR<sup>3</sup>R<sup>3a</sup>, -CF<sub>3</sub>, C<sub>1-4</sub> alkyl substituted with 1-3 R<sup>4</sup>,  
       C<sub>2-4</sub> alkenyl substituted with 0-3 R<sup>4</sup>, C<sub>2-4</sub> alkynyl  
       substituted with 0-3 R<sup>4</sup>, C<sub>3-6</sub> carbocycle substituted  
 25        with 0-5 R<sup>6</sup>, or 5-7 membered heterocycle substituted  
       with 0-3 R<sup>6</sup>; and
- R<sup>2</sup> is C<sub>1-4</sub> alkyl substituted with 0-3 R<sup>7</sup>, C<sub>2-4</sub> alkenyl  
       substituted with 0-3 R<sup>7</sup>, C<sub>2-4</sub> alkynyl substituted with  
       0-3 R<sup>7</sup>, -CF<sub>3</sub>, C<sub>3-6</sub> carbocycle substituted with 0-5 R<sup>8</sup>,  
 30        or 5-7 membered heterocycle substituted with 0-5 R<sup>8</sup>.

5 22. A compound according to claim 1 wherein:

$R^1$  is phenyl substituted with 1-5  $R^6$ , naphthyl substituted with 0-5  $R^6$ , or 5-6 membered aromatic heterocycle substituted with 0-3  $R^6$ ;

$R^2$  is C<sub>3-6</sub> carbocycle substituted with 0-5  $R^8$ , or 5-7  
10 membered heterocycle substituted with 0-5  $R^8$ ;

$R^8$  is, at each occurrence, independently selected from the group: halo, -CN, NO<sub>2</sub>, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, NR<sup>13</sup>R<sup>13a</sup>, NR<sup>13</sup>NR<sup>13a</sup>R<sup>13b</sup>, NR<sup>13</sup>C(O)OR<sup>14</sup>, NR<sup>13</sup>C(O)R<sup>14</sup>, =O, OR<sup>14</sup>, SR<sup>14</sup>, -CF<sub>3</sub>, COR<sup>14</sup>, CO<sub>2</sub>R<sup>14</sup>, CONR<sup>13</sup>R<sup>13a</sup>,  
15 NHC(O)NR<sup>13</sup>R<sup>13a</sup>, NHC(S)NR<sup>13</sup>R<sup>13a</sup>, SO<sub>2</sub>NR<sup>13</sup>R<sup>13a</sup>, and SO<sub>2</sub>R<sup>14</sup>, or when two  $R^{8s}$  are attached to two adjacent carbon atoms, the two  $R^{8s}$  may combine to form -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-; and

$R^{13}$  R<sup>13a</sup>, and  $R^{13b}$  are are, at each occurrence,  
20 independently selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl; or

$R^{13}$  and  $R^{13a}$ , together with the nitrogen atom to which they are attached, form a 5-7 membered heterocycle substituted with 0-3  $R^{16}$ .

25

23. A compound according to claim 1 wherein:

X is O or S;

$R^1$  is -NR<sup>3</sup>R<sup>3a</sup>, -CF<sub>3</sub>, C<sub>1-4</sub> alkyl substituted with 1-3  $R^4$ ;

$R^2$  is C<sub>1-4</sub> alkyl substituted with 0-3  $R^7$ , C<sub>2-4</sub> alkenyl  
30 substituted with 0-3  $R^7$ , C<sub>2-4</sub> alkynyl substituted with

5           0-3  $R^7$ ,  $-CF_3$ , C<sub>3-6</sub> carbocycle substituted with 0-5  $R^8$ ,  
or 5-7 membered heterocycle substituted with 0-5  $R^8$ ;  
 $R^4$  is, at each occurrence, independently selected from the  
group: halo,  $-CN$ ,  $NO_2$ ,  $-NR^9R^{9a}$ ,  $NR^9NR^{9a}R^{9b}$ ,  
 $NR^9C(O)OR^{10}$ ,  $NR^9C(O)R^{10}$ ,  $=O$ ,  $OR^{10}$ ,  $SR^{10}$ ,  $-CF_3$ ,  $COR^{10}$ ,  
10            $CO_2R^{10}$ ,  $CONR^9R^{9a}$ ,  $NHC(O)NR^9R^{9a}$ ,  $NHC(S)NR^9R^{9a}$ ,  
 $SO_2NR^9R^{9a}$ , and  $SO_2R^{10}$ ;  
 $R^9$  is, at each occurrence, independently selected from the  
group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;  
 $R^{9a}$  is, at each occurrence, independently selected from the  
15           group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl;  
 $R^{9b}$  is, at each occurrence, independently selected from the  
group: H, C<sub>1-4</sub> alkyl, phenyl and benzyl; or  
 $R^9$  and  $R^{9a}$ , together with the nitrogen atom to which they  
are attached, form a 5-7 membered heterocycle  
20           substituted with 0-3  $R^{16}$ ;  
 $R^{16}$  is, at each occurrence, independently selected from the  
group consisting of: halo,  $-CN$ ,  $NO_2$ , C<sub>1-4</sub> alkyl, C<sub>1-4</sub>  
haloalkyl,  $NR^{20}R^{20a}$ ,  $NR^{20b}NR^{20}R^{20a}$ ,  $NR^{20}C(O)OR^{21}$ ,  
 $NR^{20}C(O)R^{21}$ ,  $=O$ ,  $OR^{21}$ ,  $SR^{21}$ ,  $COR^{21}$ ,  $CO_2R^{21}$ ,  $CONR^{20}R^{20a}$ ,  
25            $NHC(O)NR^{20}R^{20a}$ ,  $NHC(S)NR^{20}R^{20a}$ ,  $SO_2NR^{20}R^{20a}$ , and  
 $SO_2R^{21}$ ; and  
 $R^{20}$ ,  $R^{20a}$ , and  $R^{20b}$  are, at each occurrence, independently  
selected from the group: H, C<sub>1-4</sub> alkyl, phenyl and  
benzyl.

30

5 24. A compound according to claim 1 selected from the group:

3-(4-methoxyphenyl)-5-(2-(3,5-dimethoxybenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

10 3-(4-methoxyphenyl)-5-(2-isonicotinoyl  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-nicotinoylhydrazinecarbox  
amido)indeno[1,2-c]pyrazol-4-one;

15 3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxybenzoyl)hydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(4-hydroxybenzoyl)hydrazine  
20 carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-aminobenzoyl)hydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one;

25 3-(4-methoxyphenyl)-5-(2-(4-aminobenzoyl)hydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2-aminobenzoyl)hydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one;

30 3-(4-methoxyphenyl)-5-(2-(4-N,N-dimethylaminobenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-methoxybenzoylhydrazine  
35 carboxamido)indeno[1,2-c]pyrazol-4-one;

- 5 3-(4-methoxyphenyl)-5-(2-(2-hydroxybenzoyl)hydrazine  
carboxamido)indeno[1,2-c]pyrazol-4-one; and
- 3-(4-methoxyphenyl)-5-(2-(3,5-diaminobenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 10 3-(4-methoxyphenyl)-5-(2-(1-naphthoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 3-(4-methoxyphenyl)-5-(2-amido  
15 hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 3-(4-methoxyphenyl)-5-(2-phenylamido  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 20 3-(4-methoxyphenyl)-5-(2-(4-methylbenzoyl  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 3-(4-methoxyphenyl)-5-(2-(2-naphthoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 25 3-(4-methoxyphenyl)-5-(2-(3-(4-hydroxyphenyl)propionyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 3-(4-methoxyphenyl)-5-(2-(4-methoxybenzoyl)  
30 hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;
- 35 3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

5

3-(4-methoxyphenyl)-5-(2-(2-thienoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-methylbenzoyl)  
10 hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-amino-4-hydroxybenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

15 3-(4-methoxyphenyl)-5-(2-(2,5-dichlorobenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxybenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

20

3-(4-piperazinylphenyl)-5-(2-(nicotinoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-(4-methylpiperazinyl)phenyl)-5-(2-(nicotinoyl)  
25 hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-(4-methylpiperazinyl)phenyl)-5-(2-(isonicotinoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

30 3-(4-piperazinylphenyl)-5-(2-(isonicotinoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one; and

3-(4-piperazinylphenyl)-5-(2-(3,5-dimethoxybenzoyl)  
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one; or

5 a pharmaceutically acceptable salt form thereof, a  
pharmaceutically acceptable prodrug form thereof, an N-oxide  
form thereof, or a stereoisomer thereof.

25. A pharmaceutical composition, comprising: a  
10 pharmaceutically acceptable carrier and a therapeutically  
effective amount of a compound of claim 1.

26. A pharmaceutical composition, comprising a -  
pharmaceutically acceptable carrier, a compound according  
15 to claim 1 or a pharmaceutically acceptable salt or prodrug  
form thereof, and a cytostatic or cytotoxic agent.

27. A method of treating a cell proliferative disease  
associated with CDK activity in a patient in need  
20 thereof, comprising administering to said patient a  
pharmaceutically effective amount of a compound according to  
claim 1, or a pharmaceutically acceptable salt or prodrug  
form thereof, wherein the proliferative diseases is selected  
from the group consisting of: Alzheimer's disease, viral  
25 infections, auto-immune diseases, fungal disease, cancer,  
psoriasis, vascular smooth cell proliferation associated  
with atherosclerosis, pulmonary fibrosis, arthritis  
glomerulonephritis, neurodegenerative disorders and post-  
surgical stenosis and restenosis.

30 28. A method of treating cancer associated with CDK  
activity in a patient in need thereof, comprising  
administering to said patient a pharmaceutically effective  
amount of a compound according to claim 1, or a  
35 pharmaceutically acceptable salt or prodrug form thereof,  
wherein the cancer is selected from the group consisting of:  
carcinoma such as bladder, breast, colon, kidney, liver,  
lung, including small cell lung cancer, esophagus, gall-  
bladder, ovary, pancreas, stomach, cervix, thyroid,

5 prostate, and skin, including squamous cell carcinoma;  
hematopoietic tumors of lymphoid lineage, including  
leukemia, acute lymphocytic leukemia, acute lymphoblastic  
leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's  
lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and  
10 Burkett's lymphoma; hematopoietic tumors of myeloid lineage,  
including acute and chronic myelogenous leukemias,  
myelodysplastic syndrome and promyelocytic leukemia; tumors  
of mesenchymal origin, including fibrosarcoma and  
rhabdomyosarcoma; tumors of the central and peripheral  
15 nervous system, including astrocytoma, neuroblastoma, glioma  
and schwannomas; other tumors, including melanoma, seminoma,  
teratocarcinoma, osteosarcoma, xenoderma pigmentosum,  
keratoctanthoma, thyroid follicular cancer and Kaposi's  
sarcoma.

20

29. A method of treating a disease associated with  
apoptosis in a patient in need thereof, comprising  
administering to said patient a pharmaceutically effective  
amount of a compound according to claim 1, or a  
25 pharmaceutically acceptable salt or prodrug form thereof,  
wherein the disease associated with apoptosis is selected  
from the group consisting of: cancer, viral infections,  
autoimmune diseases and neurodegenerative disorder.

30

30. A method of inhibiting tumor angiogenesis and  
metastasis in a patient in need thereof, comprising  
administering to said patient a pharmaceutically effective  
amount of a compound according to claim 1, or a  
pharmaceutically acceptable salt or prodrug form thereof.

35

31. A method of modulating the level of cellular RNA and  
DNA synthesis in a patient in need thereof, comprising  
administering to said patient a CDK inhibitory effective



5 amount of a compound according to claim 1, or a  
pharmaceutically acceptable salt or prodrug form thereof.

32. A method of treating viral infections in a patient in  
need thereof, comprising administering to said patient a CDK  
10 inhibitory effective amount of a compound according to claim  
1, or a pharmaceutically acceptable salt or prodrug form  
thereof, wherein the viral infections is selected from the  
group consisting of HIV, human papilloma virus, herpesvirus,  
poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus.

15 33. A method of chemopreventing cancer in a patient,  
comprising administering to said patient in need thereof, a  
CDK inhibitory effective amount of a compound according to  
claim 1, or a pharmaceutically acceptable salt or prodrug  
20 form thereof.

34. A method of inhibiting CDK activity comprising  
combining an effective amount of a compound according to  
claim 1, with a composition containing CDK.

25 35. A method of treating cancer associated with CDK  
activity in a patient in need thereof, comprising  
administering to said patient a pharmaceutically effective  
amount of a compound according to claim 1, or a  
30 pharmaceutically acceptable salt or prodrug form thereof,  
in combination (administered together or sequentially) with  
known anti-cancer treatments such as radiation therapy or  
with cytostatic or cytotoxic agents, wherein such agents are  
selected from the group consisting of: DNA interactive  
35 agents, such as cisplatin or doxorubicin; topoisomerase II  
inhibitors, such as etoposide; topoisomerase I inhibitors  
such as CPT-11 or topotecan; tubulin interacting agents,  
such as paclitaxel, docetaxel or the epothilones; hormonal  
agents, such as tamoxifen; thymidilate synthase inhibitors,

5 such as 5-fluorouracil; and anti-metabolites, such as methotrexate.

36. A method treating cell proliferative diseases associated with CDK activity in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, in combination (administered together or sequentially) with known anti-proliferating agents selected from the group consisting of: altretamine, busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, thiotepa, cladribine, fluorouracil, floxuridine, gemcitabine, thioguanine, pentostatin, methotrexate, 6-mercaptapurine, cytarabine, carmustine, lomustine, streptozotocin, carboplatin, cisplatin, oxaliplatin, iproplatin, tetraplatin, lobaplatin, JM216, JM335, fludarabine, aminoglutethimide, flutamide, goserelin, leuprolide, megestrol acetate, cyproterone acetate, tamoxifen, anastrozole, bicalutamide, dexamethasone, diethylstilbestrol, prednisone, bleomycin, dactinomycin, daunorubicin, doxorubicin, idarubicin, mitoxantrone, losoxantrone, mitomycin-c, plicamycin, paclitaxel, docetaxel, CPT-11, epothilones, topotecan, irinotecan, 9-amino camptothecin, 9-nitro camptothecin, GS-211, etoposide, teniposide, vinblastine, vincristine, vinorelbine, procarbazine, asparaginase, pegaspargase, methotrexate, octreotide, estramustine, and hydroxyurea.

37. A method of inhibiting CDK1 activity, comprising administering to a patient in need thereof an effective CDK1 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

- 5 38. A method of inhibiting CDK2 activity, comprising  
administering to a patient in need thereof an effective CDK2  
inhibitory amount of a compound according to claim 1, or a  
pharmaceutically acceptable salt or prodrug form thereof.
- 10 39. A method of inhibiting CDK3 activity, comprising  
administering to a patient in need thereof an effective CDK3  
inhibitory amount of a compound according to claim 1, or a  
pharmaceutically acceptable salt or prodrug form thereof.
- 15 40. A method of inhibiting CDK4 activity, comprising  
administering to a patient in need thereof an effective CDK4  
inhibitory amount of a compound according to claim 1, or a  
pharmaceutically acceptable salt or prodrug form thereof.
- 20 41. A method of inhibiting CDK5 activity, comprising  
administering to a patient in need thereof an effective CDK5  
inhibitory amount of a compound according to claim 1, or a  
pharmaceutically acceptable salt or prodrug form thereof.
- 25 42. A method of inhibiting CDK6 activity, comprising  
administering to a patient in need thereof an effective CDK6  
inhibitory amount of a compound according to claim 1, or a  
pharmaceutically acceptable salt or prodrug form thereof.
- 30 43. A method of inhibiting CDK7 activity, comprising  
administering to a patient in need thereof an effective CDK7  
inhibitory amount of a compound according to claim 1, or a  
pharmaceutically acceptable salt or prodrug form thereof.
- 35 44. A method of inhibiting CDK8 activity, comprising  
administering to a patient in need thereof, an effective CDK8  
inhibitory amount of a compound according to claim 1, or a  
pharmaceutically acceptable salt or prodrug form thereof.

- 5    45. A method of inhibiting CDK9 activity, comprising  
administering to a patient in need thereof an effective CDK9  
inhibitory amount of a compound according to claim 1, or a  
pharmaceutically acceptable salt or prodrug form thereof.
- 10   46. A pharmaceutical kit for treating a cell proliferative  
disease associated with CDK activity, said kit comprising a  
plurality of separate containers, wherein at least one of  
said containers contains a compound according to claim 1, or  
a pharmaceutically acceptable salt or prodrug form thereof,  
15   and at least another of said containers contains one or more  
compounds selected from the group consisting of cytostatic  
or cytotoxic agents, such as for example, but not limited  
to, DNA interactive agents, such as carboplatin, cisplatin  
or doxorubicin; topoisomerase II inhibitors, such as  
20   etoposide; topoisomerase I inhibitors such as CPT-11 or  
topotecan; tubulin interacting agents, such as paclitaxel,  
taxane, docetaxel or the epothilones; hormonal agents, such  
as tamoxifen; thymidilate synthase inhibitors, such as 5-  
fluorouracil; and anti-metabolites, such as methotrexate,  
25   and said containers optionally contain a pharmaceutical  
carrier, which kit may be effectively utilized for carrying  
out combination therapies according to the invention.

## INTERNATIONAL SEARCH REPORT

 Internat Application No  
 PCT/JP 00/28952

 A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 C07D231/54 C07D401/12 C07D409/12 A61K31/416 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 54308 A (DU PONT PHARM CO) 28 October 1999 (1999-10-28) compounds LXIV, CIV - CXI, CXIII, CXIV, CL page 1, line 10 - line 15; claims 1,7 -----	1-46

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

8 June 2001

Date of mailing of the international search report

19/06/2001

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

The present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The functional term "prodrug" does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of said claim. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search does not include prodrugs of the compounds of formula I.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

tion on patent family members

Internati

Application No

PCT/JP 00/28952

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9954308 A	28-10-1999	AU 3654899 A EP 1071668 A	08-11-1999 31-01-2001